Tuberculosis-associated obstructive pulmonary disease: a clinical, radiological and pathophysiological study of the contribution of previous pulmonary tuberculosis in a community-based study of chronic obstructive pulmonary disease

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Without winter, we can never fully appreciate spring.

This thesis is dedicated to my loving family
and my God – the Lord of Heaven's armies.

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……

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Abstract

Epidemiological studies in populations with a high burden of pulmonary tuberculosis (PTB), including the Burden of Obstructive Lung Disease (BOLD) survey performed in Cape Town, South Africa in 2005, have suggested an association between PTB and the development of chronic airflow obstruction (CAO). The nature of this association and mechanisms responsible for CAO has not been previously studied, but likely includes: airway narrowing (from bronchiolitis, bronchiectasis or persistent low-grade inflammation associated with healed PTB); and reduced lung elastic recoil from coexistent emphysema. The present study investigated the structure and function of the lung in subjects with tuberculosis-associated obstructive pulmonary disease (TOPD) identified in BOLD 2005, and aspects of its natural history and response to treatment. It also examined the diagnostic performance of the standardised and internationally accepted BOLD method for estimating the prevalence of COPD in community-based surveys, with specific reference to misdiagnosis that might lead to overestimates of prevalence.

The study of TOPD was based on 103 of 196 subjects identified with CAO from BOLD 2005, and re-examined in 2010. These were categorised by history and chest CT scan into three groups: no previous tuberculosis (NPTB, n=31, 30.1%); probable previous tuberculosis (PrPTB, n=33, 32.0%); or definite previous tuberculosis (DPTB, n=39, 37.8%). In spite of similar demographics, smoking history, symptoms (MRC Dyspnoea score), health status (St George's Respiratory Questionnaire score) and severity of CAO (mean post-bronchodilator FEV1, FVC and FEV1:FVC), subjects with DPTB had 16.3% lower diffusing capacity (DL_{CO}) and 22.2% lower IC, than NPTB subjects. Multivariate analysis of quantitative CT scan findings confirmed that DPTB subjects had 6.5% higher gas trapping scores, 0.3% higher fibrosis scores, and 3.5% higher emphysema scores than subjects with NPTB, while the Pi10 – a measure of airway wall thickness – was similar between groups. This pattern suggests that a major site of CAO in TOPD is the smaller airways and bronchioles. This may reflect widespread involvement of the bronchial mucosa in PTB, resulting in cicatricial narrowing and even obliteration of airways. Both ventilation:perfusion mismatch and attenuation of the pulmonary vasculature adjacent to the fibrosed bronchi may contribute to the reduced DLco.

Of the original cohort with CAO, 45 (23.0%) subjects died during the five-year follow-up period, and, on multivariate analysis, only age and GOLD stage 4 disease in 2005 predicted death. The rate of decline in FEV1 was similar in subjects with and without PPTB, as well as various severity stages

of COPD. Treatment responses were also similar in subjects with and without PPTB.

The study of the diagnostic performance of the BOLD method confirmed significant misdiagnosis. Although the questionnaires performed acceptably, CAO was not confirmed in 15.1% of the cohort at follow-up, and a similar proportion of the cohort were found to have chronic asthma, some of which had CAO. Studies of the handheld spirometer specified by BOLD (the EasyOne ndd), confirmed significant variation between tests performed on the same spirometer and in a same-day comparison with office-based spirometry. In the latter comparison, the FEV1 differed by ≥150 mL in 22.5%, resulting in reclassification of COPD status in 16.7% of subjects. Between-visit variability of spirometry performed with the EasyOne ndd, less than one month apart, resulted in reclassification of 11 of 56 subjects (19.6%), and in 16 (28.6%), the FEV1 differed by >150 mL between visits. These findings raise questions: Whether the BOLD method should base the diagnosis of COPD on one result and whether BOLD estimates of COPD prevalence should be corrected for an anticipated over-diagnosis resulting from the inclusion of subjects with asthma.

Overall, the results of the TOPD studies supported the hypothesis that chronic airflow obstruction in patients with a history of previous PTB differs in terms of pathophysiology and radiology from patients with COPD without this risk factor, and should be considered as a phenotype of COPD. This designation will ensure that it is identified and not simply passed off as a late complication of PTB, but will be the subject of further research examining aspects of its pathogenesis, prevention and effective treatment. It is hoped that this is recognised as further reason for renewed efforts to control tobacco use and tuberculosis worldwide.

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Abbreviations

% LAA:	Percentage low attenuation area (on CT scan)
% Pred:	Percentage of predicted
6MWD:	Six-minute walk distance
AFO:	Airflow obstruction
ATS:	American Thoracic Society
ATbQ:	Additional tuberculosis questionnaire
AWT:	Airway wall thickness
BD:	Bronchodilator
BMI:	Body mass index
BOLD:	Burden of obstructive lung disease
CAO:	Chronic airflow obstruction
CB:	Chronic bronchitis
Chi2:	Chi-squared test
COPD:	Chronic obstructive pulmonary disease
CRP:	C-reactive protein
CRRS:	Chest radiograph reading and recording system
CT:	Computed tomography
DALY:	Disability adjusted life year
DL_{CO}:	Diffusing capacity of carbon monoxide
DPTB:	Definite previous tuberculosis (group)
ECCS:	European Community of Coal and Steel
ECLIPSE Study:	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
ERS:	European Respiratory Society three-group analysis
ERV:	Expiratory reserve volume
FEV1:	Forced expiratory volume in 1 second
FRC:	Functional residual capacity
FVC:	Forced vital capacity
FWHM:	Full-width-at-half-maximum
GOLD:	Global Initiative for Chronic Obstructive Lung Disease
HDM:	House dust mite
HRCT:	High resolution computed tomography
HU:	Hounsfield units
IC:	Inspiratory capacity
ICS:	Inhaled corticosteroid
IQR:	Interquartile range
IFNγ:	Interferon gamma
IL-6:	Interleukin 6
LAA:	Low attenuation areas (on CT scan)
LABA:	Long acting $beta_2$ agonist
L:	Litres
LL:	Lower lobe
LLL:	Left lower lobe
LML:	Left middle lobe
LUL:	Left upper lobe
MDCT:	Multi-detector computed tomography

MMP:	Matrix metalloproteinase
NPV:	Negative predictive value
NPTB:	No previous tuberculosis (group)
OR:	Odds ratio
PEFR:	Peak expiratory flow rate
PLATINO Study:	Project for the Investigation of Obstructive Lung Disease
pMDI:	Pressurised metered dose inhaled
PTB:	Pulmonary tuberculosis
PPTB:	Previous pulmonary tuberculosis
PPV:	Positive predictive value
PrPTB:	Probable previous tuberculosis (group)
PREPOCOL Study:	Prevalencia de EPOC en Colombia
RLL:	Right lower lobe
RML:	Right middle lobe
RUL:	Right upper lobe
RV:	Residual volume
sd:	Standard deviation
SGRQ:	St George's Respiratory Questionnaire
sIL-2R:	Soluble interleukin 2 receptor
SVC:	Slow vital capacity
TB:	Tuberculosis
TLC:	Total lung capacity
TNFα:	Tumour necrosis factor alpha
UCT:	University of Cape Town
UL:	Upper lobe
VC:	Vital capacity
WHO:	World Health Organization

Chapter 1. Introduction

Chronic obstructive pulmonary disease (COPD) is now recognised as a leading cause of death worldwide; by 2030, it is predicted to rank third. In the developed world, it is closely associated with tobacco smoking and can, thus, be expected to decline as the prevalence of smoking declines. However, currently and in the future, the greatest burden of COPD is and will be experienced in low-income and middle-income countries, in part because of smoking rates but also because of the promotion of smoking by the tobacco industries in these countries. However, it is clear that other factors that are more prevalent in developing countries, either alone or together with smoking, influence both the development and severity of COPD. Recognised risk factors are: exposure to smoke from biomass-fueled fires; childhood infections; poor nutrition before birth and during infancy; and passive exposure to the smoke of parents and partners. In addition, epidemiologic studies have confirmed a link between pulmonary tuberculosis (TB) and the later development of COPD, but few studies have examined the mechanisms of disease and nature of this association, in what respects it differs from the usual form of COPD and whether it should be regarded as a distinct entity or phenotype of COPD, requiring different strategies for prevention and treatment. These questions form the basis of the present study.

The present study builds on the findings of two previous projects undertaken by researchers from the University of Cape Town Lung Institute and Desmond Tutu TB Centre (Stellenbosch University), in two predominantly low-income suburbs of Cape Town, South Africa – Ravensmead and Uitsig.

Three major observations of these projects were as follows: First, the prevalence of COPD estimated using the Burden of Obstructive Disease (BOLD) method, was higher in these suburbs than in any other of the 12 sites surveyed in other countries of the world. Second, that although the proportion of subjects reporting cigarette smoking was high, the mean total pack-year exposure of each subject was the lowest among the 12 sites,

suggesting that factors other than tobacco smoke exposure are involved. Finally, there was a strong association between a reported history of previous TB and the presence of COPD. Almost half (49.2%) of all adults over 40 years of age who reported a previous history of TB, had spirometric evidence of airflow obstruction compatible with the diagnosis of COPD.

The association between chronic airflow obstruction (CAO) and previous pulmonary tuberculosis (PPTB) has become increasingly recognised. A number of recent well-designed epidemiological surveys have confirmed the strength of this association, and some authors have concluded that PPTB is more strongly associated with CAO than either smoking or biomass fuel exposure. However, there is a difference of opinion on whether CAO in people with PPTB should be regarded as a variant or phenotype of COPD, or whether the CAO is explained by major structural damage to a large portion of the lungs with the usual features of 'fibro-cystic change' comprising: bronchiectasis, volume loss, broad bands of fibrosis and abnormal air spaces (cysts).

The research described in the present study aimed to address some of the questions concerning the relationship between healed pulmonary TB and COPD. It comprised three main parts. The first was a follow-up study, performed in 2010, of subjects diagnosed with COPD in the BOLD 2005 study, to identify those in whom features of PPTB were present, and, using detailed tests of lung physiology and high-resolution radiologic imaging of the lungs to compare and contrast features and potential mechanisms of CAO in subjects with and without PPTB. Secondly, the interval between surveys permitted a limited study of the natural history of CAO in those with and without PPTB. Finally, as there are no descriptions on how CAO associated with PPTB should be treated, and the efficacy of usual treatment for COPD, a limited trial of treatment compared responses to treatment in these groups of subjects.

The Follow-up study provided two other important and novel research opportunities. First, the opportunity to assess the diagnostic performance of the BOLD method in providing estimates of the prevalence of COPD in

community-based surveys, which is its primary use specifically to estimate the magnitude of misdiagnosis resulting from the presence of subjects with asthma in the sample. Second, to assess the performance (accuracy and repeatability) of the BOLD questionnaire and method of spirometry with the potential that this information would inform the use and interpretation of results obtained in BOLD surveys globally.

This dissertation begins with a Literature Review (Chapter 2) of COPD, specifically its prevalence, associations, phenotyping, mechanisms of disease and natural history relevant to the present study. The BOLD and other methods used in the present study are also reviewed. Chapter 3 provides the hypothesis and objectives of the work, and Chapter 4 describes detailed methodology. Chapter 5 provides data from the Follow-up 2010 study; mortality, demographics and lung physiology. The analysis of the BOLD method is provided in Chapter 6, including diagnostic accuracy and performance of the BOLD instruments. Chapter 7 is dedicated to the classification of subjects according to their PPTB status, and rationale for the final classification used. Chapters 8 and 9 present the comparison of lung physiology and imaging data, respectively, between subjects with and without PPTB. Chapter 10 provides the results of multivariate analysis of associations that point to the site of airflow obstruction in PPTB. The final chapter discusses the important findings of this study, their implications and application.

Chapter 2. Literature Review

2.1. Introduction

This review provides the background to the work described in this study beginning with a current view of the definition of chronic obstructive pulmonary disease (COPD), epidemiologic data on risk factors for COPD and evidence supporting tuberculosis (TB) as a cause of chronic airflow obstruction (CAO). It also considers the evolving field of phenotyping in COPD, mechanisms of airflow obstruction in COPD and in post-tuberculosis lung disease; and new advances in lung imaging to identify and quantitate lung pathology in COPD and its relationship to lung physiology.

2.2. Definitions of COPD

Chronic obstructive pulmonary disease is a common respiratory disorder that presents in adult life and is characterised by airflow obstruction. Historically, a number of definitions for COPD have been proposed and these have evolved with new appreciation of facts about its causation, natural history and pathophysiology.

The position paper of the combined American Thoracic Society (ATS)/European Respiratory Society (ERS) taskforce published in 2004 defined COPD as: *'Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.'*[1,2]

The NICE guidelines (UK) similarly stated: '*Chronic obstructive pulmonary disease (COPD) is characterised by airflow obstruction. The airflow obstruction is usually progressive, not fully reversible and does not change markedly over several months. The disease is predominantly caused by smoking.*'[3]

The South African Thoracic Society defined COPD as: '*a disease state resulting from an abnormal inflammatory response of the lungs to irritant particles and gases, with resultant progressive airflow limitation that is partially reversible. It is associated with lung hyperinflation and systemic effects. The pathological correlates are chronic bronchitis and emphysema.*'[4]

Finally, the most widely cited definition for COPD is that of the Global initiative for chronic Obstructive Lung Disease (GOLD), which, in 2013, defined COPD as: *'a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases."*[5]

Common to all definitions is the presence of airflow 'obstruction' or, the more accurate term 'airflow limitation' measured by spirometry. The measure of airflow limitation required to define this is a reduced ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC), but there is controversy concerning the threshold value that defines impairment.[6] Currently, there are two approaches to defining COPD using the FEV1:FVC ratio.

The first method ('fixed-ratio' method) defines irreversible airflow obstruction as FEV1:FVC <0.7, regardless of subject age. The alternative approach defines COPD using the lower limit of normal (LLN) cut-point based on predicted FEV1:FVC values from a reference population.[7] For this definition, the fifth percentile for the subject's age and gender is conventionally used as the LLN cut-point, corresponding to a standard deviation score of <–1.645 for the population. Both the fixed-ratio and LLN methods have limitations.

First, as part of the normal aging process both FEV1 and FVC decline over time but as FEV1 declines more rapidly than the FVC, the FEV1:FVC decreases with age, even in the absence of disease. Thus, using a fixed ratio cut-point will result in under diagnosis in younger subjects (whose ratio should be higher, and for whom 0.7 is lower than the LLN), and over diagnosis of COPD in the elderly (especially those over 70 years of age). For example, in a study of 71 asymptomatic, Norwegian adults, aged 70 years and older, who had never smoked, 35% were reported to have a FEV1:FVC <0.7. In those over 80 years, 50% would have been classified as having 'COPD', using the fixed-ratio method.[8] In contrast, the LLN method is a more accurate measure for defining abnormality – the presence of airflow limitation. Thus, it is argued that for clinical purposes the LLN is the more relevant measure, and correlates better with the presence of disease. For example, Akkermans *et al* demonstrated that subjects who had an FEV1:FVC above the LLN but <0.7, did not show the same accelerated decline in FEV1 observed in subjects with a ratio below the LLN. This finding supports the hypothesis that COPD is over-diagnosed when the fixed ratio method is employed, and may lead to unnecessary concern and overtreatment, particularly in the elderly.[9]

Use of the LLN definition is, however, limited by the requirement of population reference data to derive prediction equations. Such data are frequently unavailable for the population under study. Interpreting findings using reference equations from other ethnic groups may introduce inaccuracy. For example, use of the NHANES III reference equations derived from a US population, may lead to misclassification when applied to low socioeconomic African or Asian populations.

Concern about the lack of appropriate reference equations for specific populations and ethnic groups has led to recommendations for the use of the fixed-ratio definition, over the LLN definition. Organisations that have adopted this approach include: the Global Initiative for Chronic Obstructive Lung Disease (GOLD); National Clinical Guideline Centre (NICE – UK); American Thoracic Society (ATS)/European Respiratory Society (ERS); and

the South African Thoracic Society (SATS).[2–5] Two additional benefits of using the fixed ratio are the ability to directly compare different populations and the simplicity of use for clinicians working in the field.[6]

Direct comparison between the fixed-ratio and LLN methods in cross-sectional studies have yielded mixed results; with two studies demonstrating better correlation between the presence of COPD and the fixed FEV1:FVC definition,[10,11] while in two other studies the LLN definition performed better.[12,13] Unfortunately all four studies used self-reporting of COPD by questionnaire and not physician assessment as the basis for the COPD diagnosis.

Authors of the NICE guidelines have attempted to limit the number of 'normal' subjects erroneously labelled as COPD (i.e. false positives), by stipulating that, in addition to an FEV1:FVC <0.7, the FEV1 must be less than 80.0% predicted.[3] This criteria is not included in the GOLD guidelines, and subjects with an FEV1:FVC <0.7 and FEV1 >80% predicted are labelled by GOLD as stage 1 disease.[5]

The choice of spirometric criteria used to define COPD has implications on clinical patient management, epidemiological research and health planning. In clinical practice, COPD has traditionally been under recognised and spirometry has been under utilised (discussed in more detail below). This has prompted GOLD to recommend using the simpler fixed-ratio method in an attempt to promote awareness and usability (with some success), while some commentators claim that the inevitable over diagnosis is 'not a major problem'.[6] However, GOLD are at pains to emphasise that in clinical practice the diagnosis of COPD in an individual is not solely based on spirometry, but requires both exposure to a risk factor and/or symptoms. Indeed, the latest GOLD guidelines recommend an assessment of three domains: impairment (exercise capacity and symptoms), frequency (risk) of COPD exacerbations and spirometry, emphasising a departure from previous over-reliance on spirometry alone.[5]

The majority of recent, large epidemiological studies (discussed in detail below) have used the fixed-ratio method to define airflow obstruction

without consideration of symptoms, exposure, or alternate diagnoses. Such methodology is likely to overestimate disease in the elderly and underestimate it in younger subjects.[6] Additionally, diagnostic accuracy may be worsened by the inclusion of subjects with obstructive lung diseases other than COPD (e.g. asthma). Despite these criticisms, the use of the fixed ratio in epidemiological research has been defended, as above, in that it allows comparison between population groups, while the alternative use of the LLN definition requires reference ranges, which introduces potential for bias.[14] However, health planners who base their calculations on epidemiology performed using the fixed ratio in surveys need to be aware that the estimates might be inflated.[15]

A further point of contention is the use of forced vital capacity (FVC) as the denominator in spirometry (i.e. FEV1:FVC). The ERS consensus statement in 1995 proposed using the greater of either the FVC or the slow vital capacity (SVC) to define airflow obstruction.[16] Most modern guidelines – including GOLD, NICE, ATS/ERS and SATS – recommend only using FVC as the denominator to define airflow obstruction.[2–5] In normal subjects, the FVC is generally greater than a SVC; but the converse is true in those with moderate or severe airflow limitation, particularly those with air trapping (dynamic hyperinflation).[15] Thus, use of the FEV1:SVC ratio in normal subjects will under diagnose airflow obstruction, while the FEV1:FVC is associated with under diagnosis in subjects with COPD. The difference between FVC and SVC is reduced, but not abolished, by use of a bronchodilator prior to spirometry.[15]

It is debatable whether pre-bronchodilator (pre-BD) or post-bronchodilator (post-BD) spirometry should be used to diagnose COPD. Most, but not all, recent epidemiological studies have used post-BD spirometry,[14,17,18] which is recommended by GOLD and other major professional groups.[2–5] The GOLD strategy recommends the use administration of either 400 mcg of beta$_2$-agonist, 160 mcg anticholinergic or a combination thereof prior to testing. Post-BD spirometry has been shown to be more reproducible than pre-BD spirometry and a better predictor of

high-risk clinical disease (a likelihood ratio of 2.122 for pre-BD, and 1.899 for post-BD spirometry), as well as lowering the observed 'prevalence' of disease in epidemiological studies, compared with pre-BD spirometry.[3] A disadvantage of the post-BD is operational issues such as the time and cost implications of administering and waiting for maximal bronchodilation. However, interpretation of results of studies must be cautious when diagnosis of COPD is based solely on pre-BD spirometry.

The GOLD classification is the most widely used system for grading the severity of lung function impairment. GOLD stage 1 (mild disease) is defined as an FEV1 >80% predicted, GOLD stage 2 (moderate disease) as 50%≤ FEV1 <80% predicted, GOLD stage 3 (severe disease) as 30%≤ FEV1 <50% predicted, and GOLD stage 4 (very severe disease) as FEV1 <30% predicted.[5] Thus, by definition, GOLD staging requires the uses of reference equations. The Burden of Obstructive Lung Disease (BOLD) investigators elected to use this GOLD classification as well as NHANES III prediction equations to categorise severity of airflow limitation.

Vollmer *et al* have suggested an alternative to both the fixed-ratio and LLN methods for defining COPD. They proposed the adoption of a series of separate fixed-ratio cut points for different age groups. They thought that this would overcome some of the limitations of the fixed ratio definition, as well as abrogating the need for reference data. They argued that the advantage of simplicity for the fixed-ratio method is lost as soon as measurement of clinical severity or stage of disease is attempted (i.e. GOLD stage 2 or higher)[19] This recommendation has not been widely acknowledged or adopted in the literature or guidelines.

2.3. Global burden of COPD

Much work has recently been performed in defining the global burden of disease. COPD is ranked third as a cause of mortality worldwide (after ischaemic heart disease and stroke), with age-standardised death rates of

43.8 per 100 000.[20] The World Health Organization estimates that 64 million people suffered with COPD in 2004, with in excess of three million deaths occurring in 2005. Additionally, it is estimated that 90% of COPD deaths occur in low-income and middle-income countries.[21] Apart from mortality, COPD is projected to rank fifth in terms of global disease burden by 2020. As a cause of disability-adjusted life years (DALYs), COPD will be the seventh leading cause by 2030, from a ranking of twelfth in 1990.[22] Despite the high global disease burden, COPD remains a largely under-diagnosed and under-recognised condition in the general population.[23]

In the last decade, several epidemiological studies have been performed to determine the prevalence rates of COPD in various population groups. These data show significant global and regional variation, which is in part due to differences in survey methods and criteria for diagnosis.[22]

The large Burden of Obstructive Lung Disease (BOLD) initiative conducted a survey in 12 sites worldwide (n=9 425), and found the global prevalence of stage 2, or higher, COPD to be 10.1% (SE ±4.7%); 11.8% for men and 8.5% for women.[14] This study showed marked heterogeneity in the prevalence and staging of COPD across sites and between the genders, which was unexplained by age differences or smoking status of the populations, nor by other risk factors like biomass fuel and occupational exposures and tuberculosis.[24]

The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO Study) was a population-based prevalence survey conducted in five major Latin American cities (n=5 315). Menezes *et al* found the prevalence of COPD ranging between 7.8% (Mexico City) and 19,7% (Montevideo), with rates ranging from 11.4% to 22.2% for men, and from 6.5% to 14.5% for women.[25] Caballero *et al* conducted a similar population-based survey in five Colombian cities (n=5 539). This PREPOCOL (Prevalencia de EPOC en Colombia) study found an overall prevalence of COPD of 8.9%, ranging from 6.2% (Barranquilla) to 13.5% (Medellin), and men were found to have higher rates of COPD compared with women (13.6% vs. 6.6%). In addition to age and smoking status, a history of

tuberculosis, biomass exposure and low education were found to be associated with COPD.[18] In China, Lam *et al*, using the large Guangzhou cohort (n=5 522), found the prevalence of airflow obstruction to be 6.5% overall, with similar rates in both men (6.4%) and women (6.5%).[26]

Apart from the morbidity and mortality associated with COPD, the disease places a high burden upon society in terms of cost and healthcare utilisation. In the United States alone, the direct medical costs of COPD were estimated to be $15.5 billion in 1993.[27] These estimates have risen and, currently in the USA, the direct costs of COPD are estimated to be $29.5 billion and indirect costs $20.4 billion per year. In Europe, the direct costs of respiratory disease consumes 6% of the total healthcare budget, with COPD accounting for 56% (€38.6 billion) of this cost.[5] In the United Kingdom, the disease is responsible for 24 million working days being lost annually, at an estimated cost of £600 million in social security costs and £1.5 billion in lost productivity per year, in addition to the direct costs of management. Hospital care, medication and oxygen therapy account for most of these direct costs of COPD, and correlate with disease severity, age and health status of the patient. In Spain, the annual cost per patient is $1 876 per annum, with hospital costs (43%) and drugs (40%) being the major contributors. In the United States, direct healthcare costs in one cohort ranged from $1 681 (in stage 1 disease) to $10 812 (in stage 3 disease), per annum.[27] Comparative data on costs of COPD are not available for much of the developing world.

2.4. Burden of COPD in South Africa

There is also paucity of prevalence data for COPD in South and Sub-Saharan Africa. Despite this, a number of sources suggest a high burden of chronic lung diseases in the South African population. For example, according to the latest Statistics South Africa Report (2013), chronic lower respiratory diseases were the cause of 2.8% of deaths in men in 2010 (ranked eighth), and it is presumed that a significant proportion of these deaths were due to COPD. In adults between 50 and 64 years of age, chronic lower respiratory

diseases were responsible for 3.8% of deaths (ranked seventh), while in adults over 65 years they accounted for 4.4% of deaths (ranked seventh). The Western Cape had the highest rate of death due to chronic lower respiratory diseases (4.4%) when compared with the other provinces (range <1.8%-3.7%).[28]

The Lung Health Study was a community based population survey conducted in the Western Cape in 2002 that assessed the prevalence of respiratory symptoms among 3 483 people from two lower-income communities. Jithoo *et al* found that 38.3% of adults (over 15 years of age) had at least one respiratory symptom, while 18.2% of those over 40 years of age had Grade 2 dyspnoea or higher.[29] Among 13 000 subjects in the South African Demographic and Health Survey of 2004, a history compatible with chronic bronchitis was reported in 2.3% of men and 2.8% of women surveyed.[30]

Jithoo *et al* were the first researchers to perform a community-based prevalence survey of COPD in an adult South African population using standardised spirometry. This group employed the BOLD methodology and examined 847 adult subjects from two low-to-middle income suburbs in Cape Town. They reported that 23.8% of all subjects had GOLD stage 1 or higher COPD (28.7% for men, 20.0% for women), with GOLD stage 2 or higher COPD found in 19.1% of adults (22.2% for men, 16.7% for women). This was the highest rate reported among the 12 BOLD global study sites.[14,29] The Cape Town site reported very high rates of smoking in the study population, with 83.0% of men and 59.0% of women being 'ever-smokers'. These were the highest and second-highest rates, respectively, of the 12 BOLD sites studied. However, there was a discrepancy between the total numbers of 'ever-smokers' and the number of cigarettes smoked. Despite the high number of smokers, the total burden of smoking was only 18.3 pack-years for men and 15.1 for women. When compared to the other 11 bold sites this was the lowest total burden for men (BOLD range 18.3-44.9 pack-years) and the second lowest for women (BOLD range 9.3-35.5 pack-

years). In addition to smoking, higher rates of previous tuberculosis as well as occupational exposures were found.

The study by Jithoo *et al* was included in a recent systematic review on the prevalence of COPD in Sub-Saharan Africa, performed according to MOOSE (Meta-Analyses and Systematic Review of Observational Studies) guidelines. Only nine studies met eligibility criteria, of which five were from South Africa.[31] The authors reported a markedly varying prevalence of COPD between the nine studies, ranging from 4.1%-24.8%. Only the Jithoo *et al* study included a representative sample of the general population and internationally recognised case definitions. Others were either performed in a non-general population (e.g. in miners or brick-workers), or had inadequate case definitions. Varying prevalence rates are therefore attributable to differing patient populations, lack of consistent diagnostic criteria and varying quality of the methodology between the studies. The review was unable to include estimates of the economic burden of COPD in Africa, but reported marked differences in the smoking status between studies, highlighting differences in exposure risks. The current smoking rates varied between 11 and 71% for men, and 0% and 61% for women.

2.5. Risk factors for developing COPD

Cigarette smoking has long been considered the most important cause of COPD. The United States Surgeon General report in 1984 concluded that 80%-90% of COPD in the United States was attributable to smoking. However, in the last two decades, there has been increasing recognition of risk factors other than smoking as a cause for chronic airflow obstruction, especially in developing nations.[32] The increasing recognition of the heterogeneity of COPD, both in terms of risk factors and phenotypes, has opened a debate on whether or not only smoking-related disease should be termed COPD.

Those in favour of defining COPD as a purely smoking-related disease argue that although chronic airflow obstruction can undoubtedly be found in

non-smoking related disease (e.g. asthma), the mechanisms of disease and causes of airflow limitation are different from those caused by cigarette smoking. An example of this is the airflow obstruction related to domestic wood-smoke inhalation, which shows features more commonly associated with inorganic dust exposure (such as fibrosis, inflammatory focal thickening of the alveolar septae and diffuse anthracotic deposition), suggesting a possible different pathophysiology.[33] They further argue that if the term COPD is restricted to disease associated with smoking, it will encourage more extensive diagnostic workup of patients with CAO who have never smoked, thereby reducing 'misdiagnoses' of COPD. Further, by confining the term COPD to smoking-related disease, the heterogeneity of the airflow obstruction would be reduced, allowing more specific research into disease mechanisms and treatment. This view appears to be predominantly held in the developed world where other causes of CAO are few.

Estimates of non-smoking related COPD in different populations vary widely, but might be as high as 25% or even 45% of patients with COPD having never smoked.[34] The Third National Health and Nutrition Examination Survey showed that 42% of cases with airflow obstruction (defined by FEV1:FVC <0.70) were non-smokers.[35] Several other studies have supported these findings. For example, Lamprecht *et al* assessed 4 291 'never smokers' from 14 countries that participated in the BOLD study, and found 6.6% met criteria for GOLD stage 1 (mild) disease, and 5.6% for GOLD stage 2 or higher (moderate to severe COPD).[36] Significantly, in Austria, which is a developed country, nearly a third of subjects with chronic airflow limitation had never smoked.[37] There are a number of possible explanations for these findings: the first lies in the definition of COPD and methodology used to determine burden of disease. Some authors argue that using the fixed ratio (i.e. FEV1:FVC <0.70) to define COPD is in part to blame for the observation of COPD in non-smokers, especially the over-diagnosis of COPD in the elderly, as discussed above. Thus, epidemiological links between these 'false positive' subjects and non-smoking causes may be erroneously drawn.[18] A second explanation is misdiagnosis, that is, CAO being caused by a disease

other than COPD. A third possibility is that risk factors other than tobacco smoke can cause a form of lung disease, which is either entirely or partially similar to smoking-related disease. Further research is required to test the latter hypothesis, as most current research has focused on the classical form of smoking-related COPD and there is limited evidence into mechanisms in well-characterised cohorts of non-smokers with COPD

In spite of the above uncertainties, most current COPD definitions, including that of GOLD, recognise the existence of aetiological risk factors other than smoking,[22] and the American Thoracic Society (ATS) statement (2010) claims that it is erroneous to view cigarette smoking as the sole meaningful factor in the epidemiology and natural history of COPD,[32] and that a substantial proportion of COPD cases can not be explained by smoking alone, especially among young persons, females and residents of developing countries. The document lists occupational exposure, traffic, outdoor pollution, second-hand smoke, biomass exposure, dietary factors and rare genetic syndromes (such as alpha-1-antitrypsin deficiency) as possible additional causes of COPD. In addition, chronic asthma and tuberculosis are also recognised causes of irreversible airflow obstruction, but uncertainty remains as to whether these are the same as COPD in terms of clinical features and natural history.

The evidence surrounding inclusion of these factors as potential causes of COPD are considered below, particularly that relating to tuberculosis and COPD.

2.5.1. Non-tuberculosis risk factors

2.5.1.1. Smoking

It is not disputed that cigarette smoking is an important cause of COPD, and early estimates were that 15% of smokers would develop symptomatic disease.[22] [33] Buist *et al* showed a significant positive association between cigarette smoking and COPD in the multinational BOLD study, with odds ratios for COPD stage 2 or higher of 1.28 (95% CI 1.15-1.42) for women and

1.16 (95% CI 1.12-1.21) for men, for each 10-pack year increase in history of smoking.[38] However, smoking-related damage might even be present in smokers with normal spirometry. Mastora *et al*, using CT-scan analysis, showed emphysema in 40% of 144 smokers with normal spirometry, compared with none in a control group of non-smokers.[39] Eisner *et al*, in a review of studies, estimated the fraction of COPD mortality attributable to smoking to be 54% for men between the ages of 30-69 years and 52% for men aged 70 years or older. Corresponding rates for women were 24% and 19%, respectively. Attributable fractions were higher in developed countries (84% and 77% for men, and 62% and 61% for women) compared with developing countries (49% and 45% for men, 20% and 12% for women).[32] In 2000, Groenwald *et al* estimated the population attributable fraction of COPD to smoking in South Africa to be 62% overall (69% for men, 51% for women).[40]

These mortality rates from COPD have continued to rise for both male and female smokers (which is not simply an effect of ageing), and recent cohorts now show similar relative risks for death from COPD for both genders who are current smokers (25.6 for men, 22.4 for women)[41]. It has been estimated that in South Africa in the year 2000, COPD accounted for 18% of the 7 831 tobacco-attributable deaths.[40] A more recent case-control, death-registry study conducted in South Africa found that smoking was responsible for 54.6% of deaths from COPD among Coloured men; with smoking-attributable rates of 47.0% for White men and 24.4% for African men. The corresponding attributable rates for women were: 48.1% for Coloured, 42.1% for White and 11.0% for African.[42] [Smoking-attributed number of deaths was calculated as S(1-1/RR), where S was the total number of deaths in smokers.]

Studies of passive or second-hand smoke exposure have confirmed an association with the development of COPD. Apart from a temporal relationship, an exposure-response gradient exists as well as biological plausibility for a causal relationship.[32]

2.5.1.2. Biomass

It is estimated that about three billion people worldwide are exposed to smoke from biomass fuel, which represents 50% of all households and 90% of rural households. It is suggested that biomass exposure may be a more important global cause of COPD than cigarette smoking.[34] Numerous studies from around the world have confirmed biomass smoke as a risk factor for COPD,[43–46] with one systematic review estimating the odds ratio for the development of COPD in women to be 2.40 (95% CI 1.47-3.93).[47]

In 2007, Norman *et al* estimated that 20% of South African households were exposed to indoor smoke, with marked variations in different population groups. The attributable fraction of COPD from solid household fuels in South Africa was estimated to be 13.1% for men and 31.1% for women, accounting for 304 deaths for men and 721 deaths for women, and 2 957 DALYs in men and 8 920 DALYs in women.[48]

2.5.1.3. Genetic

Apart from rare hereditary causes of COPD (e.g. alpha-1-antitrypsin deficiency), there is limited but plausible evidence that an individual's response to inhaled substances (e.g. cigarette smoke) may be genetically determined and influence the development of COPD. These genetic factors are likely to be particularly important in non-smokers who develop COPD.[32]

2.5.1.4. Outdoor air pollution

Although there is much evidence from longitudinal cohorts of an association between outdoor pollution and decreased lung function in childhood and adolescents, as well as more exacerbations of COPD with increasing concentrations of air pollution, the causal relationship between pollution and the development of COPD has not been well established. Biological plausibility exists for the association. However, further robust epidemiological data is required to establish causation between air pollution and COPD.[49,34,32]

2.5.1.5. Occupational exposure

There is good epidemiological evidence of a causal relationship between occupational exposures and the development of COPD. Occupations that

have been implicated include: farming; factory work with high levels of dust, fumes and toxic gases; coal mining; hard-rock mining; tunnel, concrete and construction workers.[34] The estimated population attributable fraction for occupational exposure contributing to COPD is between 15 and 20%, depending on the population studied.[32]

2.5.2. Tuberculosis

There is increasing evidence of an association between a previous history of pulmonary tuberculosis (TB) and the development of chronic airflow obstruction (CAO).

Several large population-based epidemiological studies have confirmed the association between TB and CAO. The PLATINO study, conducted among 5 571 subjects in Latin America, found CAO in 30.7% of subjects with a history of TB, compared with 13.9% among those without such history.[17] After adjusting for confounders, men with a history of TB were 4.1 times more likely to have CAO than those without a history (adjusted odds ratio for women was 1.7). In a similar population-based study performed among 5 539 subjects in Colombia (PREPOCOL Study), 25.8% of subjects with a history of TB had CAO. This association between TB and airflow obstruction was greater than that for smoking after adjusting for confounders (OR 2.94, 95% CI 1.58-5.49).[18] Additionally, in a large Chinese population study of 8 066 subjects that defined previous TB status using chest X-rays, TB was found to be independently associated with CAO, after adjustment for gender, age and smoking (OR 1.37, 95% CI 1.13-1.67).

In contrast to these results, the multinational BOLD study was unable to find an association between previous TB and CAO. Although on univariate analysis a significantly higher prevalence of previous TB was found among never-smokers with airflow obstruction than in never-smokers without airflow obstruction, this association was not significant on multivariate analysis. The reported odds ratio among never-smokers was 1.47 (95% CI 0.69-3.12) in women, and 1.65 (95% CI 0.43-6.34) in men.[14,36] The lack of a positive association in the above BOLD study is likely to be due to a dilution effect of pooling the odds ratios of all sites. Of the 14 countries included in the study,

the median prevalence for tuberculosis was only 10.45/100 000 population (range 2.4-782/100 000), compared with the global average prevalence of 201/100 000 at that time. Only two of the countries included had a prevalence of TB higher than the global average.[50] Jithoo *et al*, in the South African study that formed part of this analysis, found a strong association between previous TB and CAO. For GOLD stage 1 and 2, they reported an OR of 2.6 (95% CI 1.5-4.6), and for GOLD stage 3 and 4 an OR of 8.9 (95% CI 4.2-18.9).[29] In the Philippines, the other high burden country included in the BOLD Study, Idolor *et al* performed a separate population-based survey among 1 188 subjects from two rural areas using the BOLD methodology. These investigators similarly found a strong association between previous TB and CAO (OR 6.31, 95% CI 2.67-15.0), which was stronger than that for smoking, farming or biomass exposure.[51]

A recent review of the English language peer-reviewed literature found 19 studies addressing the association between TB and CAO (one case series, three case-control studies, four cohort studies, eight single-centre cross-sectional studies and three multi-centre cross-sectional studies).[52] Although the authors were unable to perform a meaningful meta-analysis due to the marked heterogeneity between studies, they found convincing confirmatory evidence of a positive association between a history of previous TB and CAO. Only two of the 19 included studies didn't report a positive association.

In another review comprising only South African studies, Ehrlich *et al* concluded that chronic chest symptoms and loss of lung function were consistently associated with pulmonary TB, with an OR for chronic bronchitis between 1.5 and 7.2, and an OR for spirometrically defined COPD between 2.6 and 8.9.[53] Unfortunately, only one of the eight included studies (Jithoo *et al*) employed spirometric data and was performed in a community setting. The other seven were conducted in an occupational setting (e.g. miners, bakery workers).

This association between previous TB and the development of COPD is increasingly being accepted by the international community, as

evidenced by the inclusion of TB among the risk factors for COPD in the latest GOLD guidelines.[5] However, many aspects of this association need to be studied: first, the magnitude and determinants of the risk; second, the pathophysiology, including the relationship between structural damage and lung function; and third, the natural history of PTB-associated CAO (whether CAO progresses over time) and its response to conventional treatments for COPD.

There is a paucity of prospective population-based cohort studies following subjects longitudinally into the post-TB period. Snider *et al* performed a cross-sectional study of 1 403 patients who were discharged from a TB sanatorium between 1964-1966 following completion of treatment. He reported a reduced FEV1:FVC in 42% of patients (23% obstruction, 19% mixed obstruction/restriction) upon discharge.[54] Similarly, Plit *et al* studied 74 patients who were hospitalised for TB, and reported airflow obstruction in 21 patients (28%) at completion of treatment. Thirteen of these 21 patients (62%) did not have airflow obstruction at the start of treatment.[55] In a study performed in a tertiary centre in India, 46% of 100 patients fully treated for pulmonary TB developed airflow obstruction. The severity of obstruction was mild (FEV1 >60%) in 75%; moderate (FEV1 40%-59%) in 10%; and severe (FEV1 <40%) in 15%.[56] And, in a retrospective cohort, Willcox *et al* found airflow obstruction in 68% of 71 patients treated for TB, followed up after an average of 5.6 years.[57]

It is also uncertain what fraction of COPD is attributable to previous TB. Since a large proportion of patients who develop PTB are also smokers and may have other risk factors, correction for these have been carried out. For example, Ehrlich *et al* estimated the population attributable fraction for TB in COPD to be 24.9%.[53]

Given the paucity of data, it is currently difficult to make accurate estimates as to the burden of CAO secondary to TB in South Africa; however, if extrapolation is made from the available cohort studies, it can be postulated that a significant proportion of subjects with previous TB may be affected.

2.6. Burden of pulmonary tuberculosis

Assessment of the magnitude of the TB epidemic - both globally and locally – is required in order to inform estimates on future chronic lung disease related to incident tuberculosis.

In 2012, according to the World Health Organization (WHO), there were 8.6 million cases of TB with 1.3 million deaths worldwide. Over 95% of these deaths occurred in low-income and middle-income countries.[58] The global incidence rate is estimated to be 122/100 000 population, with the average incidence rate for Africa being 255/100 000 population. Africa has the highest incidence rates of all WHO regions, with the lowest rates reported in the Americas (29/100 000 population). India, which has a population of 1.24 billion, reported the highest number of TB cases in 2012 (1.47 million cases), with an incidence rate of 176/100 000 population. China, with its population of 1.38 billion, had the second highest number of cases in 2012 (900 678 cases), with an incidence rate of 73/100 000 population.[59]

South Africa, with a population of 52 million, has a disproportionately high burden of TB. Tuberculosis was the leading cause of death in 2010, accounting for 12% of all deaths.[28] In the 2012 report, South Africa had the third highest number of cases annually (349 582 cases), behind only India and China. Additionally, South Africa had the second highest incidence rate for TB (1 003/100 000 population).[59] Only Swaziland has a higher rate (1 350/100 000 population).

In the Lung Health Study of 2002, performed in two low-income suburbs of Cape Town, 9.7% of 3 483 adults (>15 years of age) reported a previous episode of TB (12.0% for men, 8.0% for women).[29]

Based on these figures for pulmonary TB in South Africa and the association of PTB with the development of CAO, it should be anticipated that PTB might account for a heavy burden of chronic lung disease and particularly of COPD in South Africa. However, to date there are few studies that have adequately quantified this burden.

2.7. Natural history of COPD

The present study will also explore the natural history of COPD, by examining the status of patients diagnosed with COPD in the BOLD 2005 study five or more years later. First, it is relevant to review current evidence and views on this topic.

2.7.1. Lung function decline

As COPD is a disease characterised by chronic airflow limitation, FEV1 decline is the standard method for assessing deterioration in COPD. Obvious advantages of this method are its ease of measurement and reproducibility. The annual decline in normal subjects is estimated between 15-30 mL/yr.[60] Populations of normal subjects usually include smokers. A decline of approximately 35 mL/yr has been reported in a group comprising 30% current smokers.[61] In a much-cited study, Fletcher and Peto studied lung function in 792 West London men, and hypothesised that many smokers would not develop airflow obstruction. For those that did ('susceptible smokers'), the loss of lung function was greater than either non-smoking individuals or those that had ceased to smoke. They also claimed that large irreversible declines in FEV1 were very rare, and that FEV1 declined smoothly and continuously over an individual's life.[62] In the light of more recent work, the validity of these findings has been questioned. Criticisms of the Fletcher-Peto study revolve around the lack of standardisation of spirometry, high rates of loss to follow-up (likely healthy subjects) and flawed statistical analysis.[63]

More recent studies have shown lung function decline in COPD to be heterogeneous. The ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study of 2 163 patients with COPD over three years showed a mean rate of FEV1 decline of 33 ± 2 mL/yr, with significant variation between patients (sd 59 mL/yr). A total of 38% had a

decline in FEV1 >40 mL/yr, 31% a decline between 21-40 mL/yr, 23% ranged from a decline of 20 mL to a gain of 20 mL, and 8% had an increase of >20 mL/yr.[64] However, these results were possibly affected by treatment received during the course of the three-year follow-up. In a second study of 1 198 COPD patients followed for a median of 64 months and up to 10 years, Casanova *et al* showed that most (72%) showed no statistically significantly decline of FEV1. The remaining 18% showed a decline of
–86 mL/yr (95% CI –32 to –278 mL/yr).[65] In other longitudinal studies, rates of annual FEV1 decline of between 40 and 55 mL/yr have been reported.[66–68]

Lung function decline appears to be more rapid in patients with mild COPD. This hypothesis is supported by study of the placebo-treated groups in the large TORCH and UPLIFT studies.[68,69] In these studies, the decline was most rapid in heavy smokers with only mild airflow limitation at baseline. Findings in the ECLIPSE study were similar. The mean rate of decline was ± 35 ± 1 mL/yr for GOLD stage 2 patients, ± 33 ± 1 mL/yr in GOLD stage 3, and ± 25 ± 2 mL/yr for GOLD stage 4. ($p=0.170$ for stage 2 vs. stage 3, and $p<0.001$ for stage 2 vs. stage 4).[64] This 'reverse racehorse' phenomenon was also observed in a study of male smokers, the majority of whom had either mild or no COPD. The greatest decline of lung function occurred in those without airflow limitation (i.e. FEV1:FVC >0.70).[63]

A number of factors may influence lung function decline. Smoking (in particular, current smoking) is most strongly associated with accelerated decline in FEV1. Vestbo *et al* estimated this to be an additional 21 ± 4 mL/yr for current smokers compared to former smokers, while cumulative tobacco exposure (i.e. pack-years) did not appear to increase the rate of decline.[63,64] In keeping with these findings, the Lung Health Study found less lung function decline in people who quit smoking compared with those who continued to smoke (30.2 mL/yr vs. 66.1 mL/yr of FEV1 for men).[70]

Acute exacerbations of COPD have also been shown to accelerate the decline in FEV1. In the ECLIPSE study, subjects with frequent exacerbations had a mean loss of 2 ± 0.5 mL/yr per exacerbation. In the Lung Health Study, for each lower respiratory tract illness per year the FEV1 declined by an

additional 7 mL/yr,[71] while Donaldson *et al* reported a decline of 2.9 mL/yr in frequent exacerbators, compared with 0.7 mL/yr for infrequent exacerbators.[61]

Patients with chronic bronchitis have not been found to have a faster rate of decline in FEV1, but have a lower mean FEV1. An excess decline in FEV1 of 13 ± 4 mL/yr has also been found in COPD patients with more than 10% emphysema on CT scan, while bronchodilator reversibility to salbutamol was associated with both an increased loss of 17 ± 4 mL/yr and a higher mean baseline FEV1. Vestbo *et al* additionally found neither age nor gender predicted accelerated decline in FEV1 in the ECLIPSE study.[64]

However, it is argued that in COPD that monitoring change in FEV1 may not be the best method of assessing disease progression. In longitudinal studies, there is high variability in the rate of change in FEV1 between individuals, with some patients changing between severity groupings (both upward and downward migration). Furthermore, FEV1 as a test demonstrates a high variance, estimated at approximately 55 mL.[72] In COPD, spirometric values explain less than 10%-25% of patient symptoms, quality of life and exercise performance,[73] and are only weakly correlated with dyspnoea and exercise limitation.[74] Symptoms of dyspnoea and exercise limitation have also been shown to worsen over time in COPD patients, and the BODE (body mass index, obstruction, dyspnoea and exercise limitation) index demonstrated greater sensitivity in predicting mortality than FEV1 alone.[74] In patients with an FEV1 <50.0% predicted, changes in exercise tolerance (e.g. six-minute walk distance) decline more over time than FEV1.[65] It is argued that because dyspnoea worsens over time, predicts mortality and improves with therapy, it may be a better marker of disease progression in COPD than FEV1. However, there is no 'gold-standard' measurement/tool for following changes in dyspnoea. Multi-dimensional dyspnoea measurements (e.g. Transitional Dyspnoea Index (TDI), Chronic Respiratory Disease Questionnaire (CRQ), or UCSD shortness of breath questionnaire) have been shown to be better than other uni-dimensional measurements (e.g. modified Medical Research Council (mMRC) scale or Oxygen Cost Diagram (OCD)) in

COPD.[75] In spite of this, the mMRC and, more recently, the CAT method (which combines dyspnoea and exercise limitation), have been proposed by GOLD for quantitating symptom progression.

2.7.2 Predictors of mortality

FEV1 correlates inversely with mortality,[76] [77] but compared to dyspnoea and health-status scores is a weak predictor of death.[78] It performs better as a prognostic indicator when combined with other clinical data in a multidimensional index (e.g. BODE index). For every one point increase in BODE score, the hazard ratio for death from a respiratory cause is 1.62 (95% CI 1.48-1.77).[78] Variations of the BODE index have also been found to be good predictors of mortality.[73]

Older age is also consistently associated with mortality in COPD [76,77,79,80], as is chronic bronchitis, independent of the severity of obstruction.[81] Bronchiectasis in subjects with moderate-severe COPD has equally been associated with an increased risk of death, with one study of 201 subjects demonstrating a hazard ratio for death of 2.54 (95% CI 1.16-5.56) for bronchiectasis diagnosed on CT scan, after adjustment for confounders.[82]

Numerous studies have demonstrated a positive association between mortality rates and acute COPD exacerbations.[83,79,80] There is excess mortality in the weeks following a COPD exacerbation, and every new exacerbation increases the risk of subsequent mortality. For example, the risk of death is five times increased following the tenth, compared with the first hospitalisation.[83]

Other physiological parameters have been shown to predict mortality in patients with COPD. These include the diffusion capacity for carbon monoxide (DL_{CO}), and partial pressure of oxygen in the arterial blood (PaO_2).[77] The DL_{CO} is thought to represent gas transport across the alveolar–capillary membrane and is therefore influenced by the degree of emphysema, which causes parenchymal destruction and loss of the pulmonary capillary bed. Additionally, a lower total lung capacity (TLC) and raised residual volume (RV)

have been shown to predict mortality in the large NETT (National Emphysema Treatment Trial) study.[76]

A number of investigators have attempted to identify biomarkers that predict outcomes in COPD. The ECLIPSE investigators identified a subgroup of patients with persistently raised biomarkers (16% of 1 755 subjects). This 'inflamed' subpopulation of COPD exhibited increased mortality and exacerbation frequency, despite having similar lung function, compared to 'non-inflamed' subjects.[84] Although many biomarkers have been assessed, it is still unclear as to which is most useful in predicting outcomes. An increase in highly sensitive C-reactive protein (CRP) is common in COPD, but results differ between studies.[80] In the ECLIPSE Cohort, an association between white blood cell count (WBC), IL-6, IL-8, fibrinogen, CCL-18/PARC, CRP and SP-D and mortality was observed over three years. However, when added to clinical models, only IL-6 was found to improve the predictive power of the model. The other variables only added marginal improvement, and were not recommended for inclusion.[80]

2.8. Phenotyping in COPD

One of the hypotheses of the work reported in this thesis is that tuberculosis-associated chronic airflow obstruction (TOPD) differs in terms of pathophysiology, natural history and responsiveness to treatment from COPD without this risk factor. In essence, it is proposed that TOPD should be considered a distinct phenotype of COPD. This literature review will review current thinking on phenotyping in COPD.

2.8.1. Need for phenotyping

A phenotype is defined as a set of observable characteristics of an individual that result from an interaction of its genetic make up with the environment. It is now well recognised that COPD is a complex syndrome, exhibiting both pulmonary and extra-pulmonary disease.[73] The clinical manifestations and

disease course are highly variable (as highlighted above), with severity of airflow obstruction unable to capture this heterogeneity.[85] Heterogeneity of lung function decline was highlighted in the ECLIPSE study, and was discussed above. However, this heterogeneity with COPD is not merely in terms of lung function or survival but also in clinical presentation, physiology, imaging and response to therapy.[73] This has prompted an intensive search for COPD phenotypes.

There is, however, little consensus on what constitutes a phenotype. Han *et al* have proposed the following definition: 'a single or combination of disease that differ between individuals and that relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression or death)'.[73] Individuals in the same phenotypes may have similar biological and physiological mechanisms, and respond similarly to the same therapy. According to these authors, placing the emphasis on 'clinically meaningful outcomes' will necessitate the prospective validation of candidate phenotypes, prior to their adoption.[73,85]

It is evident that not all patients with COPD respond equally to all therapies. Therefore, one of the central drivers of phenotyping in COPD is to identify subsets of patients who share a common mechanistic pathway. This may allow development and trial of therapies that may be effective for such a subset, but useless (or even detrimental) for other subsets of patients.[72,86]

Currently, there is no widely accepted classification of COPD phenotypes. Owing to the marked heterogeneity of disease and its comorbidities, some have proposed that there should be '328 million phenotypes' (the number of estimated patients worldwide).[86] Different approaches to phenotyping patients with COPD will be briefly reviewed.

2.8.2. Phenotyping by exposure

COPD can be sub-classified according to the primary environmental agent deemed responsible for the airflow obstruction in the individual patient. It is likely that airflow limitation resulting from a similar cause will, to some degree, be mechanistically similar, with similar outcomes among individuals.

It is on this basis that Miravitlles and Morera argue that the term COPD should be reserved for smoking-related disease;[33] this view is not widely held.

2.8.3. Clinical phenotyping

A number of different clinical phenotypes have been proposed. A brief discussion of a number of these follows.

2.8.3.1. Chronic bronchitis

Chronic bronchitis (CB) is defined as a chronic cough with sputum production for at least three months per year, in two consecutive years. It is common in COPD, occurring in 14%-74% of patients; the prevalence in the ECLIPSE study was 35%.[64,81] Chronic bronchitis is also found in 4%-22% of never-smokers, suggesting causes other than smoking, including biomass exposure, as well as dust and chemical fume exposure.[81] Evidence from many sources have confirmed that CB is associated with more respiratory symptoms, worse quality of life, increased risk of COPD exacerbations, faster decline in FEV1 and possibly an increased all-cause mortality.[81,87–92] However, in the ECLIPSE study CB was not associated with a faster decline in FEV1, but patients with CB did have a lower mean FEV1
(43 mL ± 20 mL),[64] nor was CB associated with more frequent COPD exacerbations.[93] However, the utility of the chronic bronchitis phenotype is supported by the finding that the PDE4 inhibitor roflumilast reduces exacerbation risk in COPD patients with chronic cough (CB), but not those without.[94]

2.8.3.2. Allergic phenotype

An allergic phenotype of COPD has been proposed, comprising smokers (or ex-smokers) with airflow obstruction and no previous diagnosis of asthma, who have either hay fever or allergic upper respiratory symptoms, or allergic sensitisation to perennial allergens. In a recent study, using two separate cohorts (NHANES III, and COPD and domestic endotoxin (CODE) cohorts), Jamieson *et al* found an increased risk of COPD exacerbations and increased

respiratory symptoms in such subjects.[95] Additionally, bronchodilator reversibility (defined as a change in FEV1), although more commonly thought of in the context of asthma, has been reported in a significant proportion of COPD patients. In the NETT cohort, 22.2% of patients were found to have bronchodilator reversibility on at least one occasion. Airway hyper-responsiveness is associated with a greater decline in lung function, while subjects with greater radiological emphysema exhibit less bronchodilator reversibility. However, use of both bronchodilator reversibility and airway hyper-responsiveness in diagnosing this phenotype is limited by their high degree of variability, which have both been observed to change over time within individual patients.[73,96]

2.8.3.3. COPD/asthma overlap

Many patients with chronic airflow limitation exhibit characteristics of both asthma and COPD, and present a challenge to clinicians in both diagnosis and management. Various definitions have been proposed, one example is: the COPD/asthma overlap where 'the diagnosis of COPD (is made) in a patient with a history of previously diagnosed asthma before the age of 40 years.'[86] In a recent consensus document from Spain, this diagnosis requires two major and two minor criteria to be present. Major criteria are: very positive bronchodilator test (increase in FEV1 ≥15.0% and ≥400 mL); eosinophilia in sputum; and a personal history of asthma. Minor criteria are: high total IgE; a personal history of atopy; and a positive bronchodilator test (increase in FEV1 ≥12% and ≥200 mL) on two or more occasions.[97] In contrast, the recent combined GINA/GOLD statement on asthma-COPD overlap syndrome (ACOS), promotes a stepwise approach where clinicians weigh evidence for and against both diagnoses of asthma and COPD. If there is similar evidence for both asthma and COPD, a diagnosis of ACOS should be considered, however rigid diagnostic criteria in diagnosing ACOS are not promoted.[98] Because of a lack of a consensus definition, the true prevalence of this overlap phenotype is not known, but estimates range from 13% (COPDGene cohort)[99] to 23% of patients in their sixth decade, with the prevalence increasing with age.[100] Importantly, for this phenotype, experts

recommend that inhaled corticosteroids be started early, and that caution be exercised when withdrawing inhaled corticosteroids abruptly.[97]

2.8.3.4. Rapid and slow progression of COPD

Patients with a greater than average decline in FEV1 have been proposed as an additional phenotype. These 'rapid progressors' have higher rates of morbidity, mortality and hospitalisation. Additionally, they have been shown to have a distinct biomarker signature. What is uncertain is the absolute level of FEV1 decline that denotes a rapid progressor. Moreover, it is unclear whether the observed 'rapid decline' is merely the observable outcome of another occult process, rather than being a distinct phenotype in its own right. Rapid progressors require close monitoring of lung function over a prolonged period (at least three years); no specific treatment is currently available for these patients.[64,73,74,86]

2.8.3.5. Frequent exacerbators

There is increasing appreciation of the 'frequent exacerbator' phenotype, which refers to a patient with two or more exacerbations per year.[86] The diagnosis is usually made on self-reporting (recall) by the patients, which has been shown to be reliable. In the large ECLIPSE study, Hurst *et al*, found that some patients were susceptible to exacerbations, irrespective of disease severity. Self-reporting of previous exacerbations identified these individuals, and susceptibility of exacerbations was relatively stable over the three-year study period. Of their cohort, 22% of patients with stage 2 disease had frequent exacerbations, while 33% and 47% of stage 3 and 4 disease, respectively, had frequent exacerbations.[93] Frequent exacerbators demonstrate: a greater decline in FEV1; worsening health status; more frequent admissions to hospital; and a longer duration of stay once admitted.[61,73,83] Exacerbations are additionally associated with severity in COPD, being more frequent and severe in those with advanced disease. Moreover, a history of exacerbations appears to be the best predictor of future exacerbations, leading to the proposal of a specific 'frequent exacerbator' phenotype.[93] The interval between exacerbations decreases

with each sequential episode, being around five years between the first and second episode, and declining to less than four months between the ninth and tenth episodes. The risk of subsequent exacerbations also increases, being three-fold after the second severe exacerbation and 24-fold after the tenth severe exacerbation. Additionally, mortality appears to peak in the first week after a severe exacerbation (estimated at 40 deaths per 10 000/day), and decreases gradually over three months (estimated at five deaths per 10 000/day).[83] Interestingly, in the ECLIPSE study there was no association between exacerbations and smoking status.

2.8.4. Phenotyping based on imaging

The increasing use of CT scanning in COPD and the development of quantitative techniques for analysis has resulted in phenotyping based on imaging, or in which imaging forms a major component.

2.8.4.1. Emphysema

Increasing emphysema scores quantitated on CT scan are associated with both a worse health status and increased mortality.[73,101] The NETT (National Emphysema Treatment Trial) investigators found increased mortality if emphysema was homogeneous, or if subjects had a greater proportion of emphysema in the lower lung zones, compared with the upper zones. These patients had worse outcomes with lung volume reduction surgery than subjects with predominantly upper lobe emphysema.[76,102] These observed differences in mortality and therapeutic options, based on the presence and location of radiological emphysema, validate the use of this phenotype.

2.8.4.2. Bronchiectasis

Bronchiectasis is an abnormal, permanent dilation of the airways and causes a cycle of inflammation, infection and repair, which leads to permanent damage and destruction to the bronchial walls; it is not uncommon in COPD. In a prospective Spanish cohort, 57.2% (115 of 201 subjects) of patients with moderate-to-severe COPD (GOLD stage 2 or higher) were found to have bronchiectasis on CT scan of the chest. In addition, bronchiectasis was

independently associated with all-cause mortality (HR 2.54, 95% CI 1.16-5.56, p=0.02).[82] Patel *et al* found bronchiectasis in 50% (27 of 54 subjects) of their cohort, and showed an association between lower lobe bronchiectasis and more severe exacerbations, as well as increased bacterial colonisation and inflammatory cytokines in the sputum.[103] The presence of bronchiectasis on CT scan has been suggested as an additional phenotype, or poor prognostic marker in COPD.[73]

2.8.5. Systemic disease and inflammation

Systemic inflammation is not present in every patient with COPD. In the ECLIPSE cohort, 16% of subjects had persistent, systemic inflammation, defined on the basis of six inflammatory biomarkers: white blood cell count, CRP, IL-6, IL-8, fibrinogen and TNFα. These 'inflamed' subjects exhibited increased all-cause mortality and exacerbation frequency compared with 'non-inflamed' subjects, despite similar lung function impairment.[84] The authors were able to characterise the systemic inflammatory network pattern (inflammome) in patients with COPD, and contrasted it with the inflammome in smokers with normal lung function, as well as non-smokers. Additionally, they were able to show that systemic inflammation is not invariable in COPD, being absent in approximately a third of subjects. The mechanisms responsible for the presence and severity of inflammation and appropriate therapies are not yet known.[73,86] Despite this, Augusti *et al* proposed the 'systemic inflammatory' as a phenotype for future research.

Comorbid (systemic) disease is often found in subjects with COPD, and includes cardiovascular disease, metabolic syndrome, osteoporosis, depression and muscle wasting.[73] It is debated whether systemic comorbidity should be considered in all patients with COPD, or whether it should be considered as different phenotypes.[86] Vanfleteren *et al*, using the CIROCO (CIRO CO-morbidity) cohort, examined 13 comorbidities in 213 patients. A total of 98% of all subjects had at least one comorbidity, while 54% had more than three comorbidities. These authors identified five comorbidity clusters: less comorbidity, cardiovascular, cachectic, metabolic

and psychological. Despite disease severity being similar among the clusters, there were marked differences in health status, suggesting that comorbidity clusters may provide information additional to usual measured parameters (e.g. FEV1, exercise capacity and BODE index). Additionally, increased levels of TNF-receptors were found in the metabolic cluster, while increased levels of IL-6 were found in the cardiovascular cluster.[104]

2.8.6. Future direction

The field of phenotyping in COPD is still emerging, and for candidate phenotypes to be adopted their usefulness in predicting meaningful outcomes (e.g. symptoms, rates of exacerbations, response to therapy, rate of disease progression or death) must be confirmed. This may be achieved in longitudinal validation studies. Thereafter, biological or molecular characterisation may be attempted, with the hope of developing therapies appropriate for that phenotype.[73] Thus, phenotyping in COPD is likely to be a dynamic field in the foreseeable future, with numerous candidate phenotypes being presented, some which may endure, while others will be discarded as irrelevant.

2.9. Causation between TB and COPD

Although there is a strong epidemiological association between previous pulmonary TB and chronic airflow obstruction (CAO), this does not necessarily prove causation. (i.e. pulmonary TB as the cause of CAO/COPD). This section deals with the theory of causality and specifically focuses on temporality, confounders and reverse causation, with respect to the relationship between TB and CAO.

2.9.1. Hill's criteria for causation

In a landmark thesis on association and causation, Sir Bradford Hill presented criteria for assigning causation between an environmental factor and disease, they are:[105]

- Strength of association – the stronger the association, the greater the likelihood of causation. As discussed earlier in the present study, tuberculosis has been shown to have a strong association with CAO, even demonstrating a stronger association than that for smoking in some studies.[18]
- Consistency of evidence – the association is repeatedly observed in different places, circumstances and times. For tuberculosis, the evidence appears to be consistent in a wide variety of population groups, as discussed above.[52]
- Specificity of association – causation is suggested if an association is shown between a very specific population, and specific types and sites of disease, without another likely explanation. The more specific the association, the greater the likelihood of causation. However, Hill cautions against overemphasis of this criterion, and states that causation may still be assigned in the absence of specificity. This is because many diseases (e.g. COPD and CAO) may have more than one cause (e.g. smoking, biomass fuel, occupational exposure etc.).
- Temporality – 'which is the cart and which is the horse?' Exposure to the cause must occur before the effect; this is especially important in diseases that develop slowly. This will be further discussed in more detail below.
- Biological gradient – if the magnitude of association increases with increasing exposure, then causation may be present. This is not required in all cases, as single exposure may be enough to result in disease (e.g. HIV exposure resulting in AIDS).
- Plausibility – presence of a biologically plausible mechanism linking cause to effect. Biological plausibility is dependent upon the biological knowledge of the day, and so is not always convincingly fulfilled.

- Coherence – in assigning causality, there should be coherence between the available epidemiological and laboratory/biological data, recognising that current basic science/laboratory data and techniques may be inadequate, and coherence may lag decades behind epidemiological observations.
- Experiment – can an experiment prove the association? For example, blocking an exposure or intervening to reduce the outcome of interest.
- Analogy – is there a similar model of disease, either in humans or animals, with which the current hypothesis can be compared?

Hill did not believe that these criteria must be rigorously obeyed before accepting causality, rather he states: 'none of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us make up our minds…'

2.9.2. Temporality and biological gradient

Owing to limitations of study design, the present study is unable to address the question of temporality in the association between previous TB and CAO. However, there is published evidence to support the temporal hypothesis that incident TB predates the onset of airflow obstruction.

A number of studies conducted on patients with active TB have demonstrated airflow obstruction. Estimates of airflow obstruction among subjects with active disease have ranged from 11%-51%.[55,106–112] In addition, combined obstruction and restriction (defined as FEV1:FVC <0.7 and FVC <80% predicted) in PTB is high.

However, there is less data on the development of airflow obstruction during the treatment of TB. In a hospitalised cohort of patients with first episode pulmonary TB (n=74), Plit *et al*, found at diagnosis that 11% (n=8) of subjects had airflow obstruction. This had increased to 28% (n=21) at treatment completion, thus implying 62% of airflow obstruction developed during treatment.[55] Interestingly, restriction on lung function declined from

57% at diagnosis to 24% after completion of treatment. Snider *et al* reported obstruction at treatment completion in 23%, and mixed obstruction/restriction in a further 19% of 1 403 subjects discharged from a TB sanatorium.[54] In an Indian study, Brashier *et al* found obstruction in 46% of 100 patients at treatment completion.[56] Unfortunately, neither of the last two studies stated the prevalence of obstruction at treatment initiation, making it difficult to determine when in the course of disease and treatment airflow obstruction developed.

There is some evidence that decline in lung function and obstruction may continue after successful treatment of pulmonary TB. Hnizdo *et al* conducted a retrospective review of 27 660 gold miners and found that lung function declined after completion of treatment for pulmonary TB. They reported greatest loss of function at six months after the diagnosis of TB, which had stabilised by 12 months.[113] This study, unfortunately, only assessed FEV1 and FVC, not FEV1:FVC, neither did it adjust for either smoking or silica exposure. These weaknesses limit the conclusions that can be drawn with regards to airflow obstruction. In another retrospective review of 115 subjects who had completed TB treatment, Chung *et al* demonstrated a continued decline in lung function (both FEV1:FVC and FEV1) for 18 months following treatment completion, with some improvement thereafter.[114] The retrospective nature of this study, lack of longitudinal data and potential for selection bias, again limit the conclusions drawn. Vargha followed up 99 patients for 15 years after hospital discharge; 35% of patients developed new airflow obstruction, while airflow obstruction resolved in 12%.[115] Again, there was no adjustment for smoking. Therefore, the available literature suggests that previous TB usually antedates the development of airflow obstruction, but questions regarding the timing and subsequent progression of airflow obstruction remain.

Evidence for a biological gradient in the TB-CAO association would require that subjects with either more extensive TB or recurrent episodes of TB have more-severe airflow obstruction. Biological plausibility of the association is discussed in more detail below [see 2.10.2.1].

Hnizdo *et al*, using a cohort of gold miners, observed in patients with several episodes of active PTB that lung function declined with each episode. The decline in FEV1 was three times greater after the third episode than after the first (–410 mL vs. –153 mL). The percentage of subjects with FEV1 impairment (FEV1 <80% predicted) in those with one, two and three episodes of TB was 18%, 27% and 35%.[113] Although FEV1:FVC was not reported, the absolute loss of FEV1 (in mL) was greater than that of the FVC for all subjects who had TB, regardless of the number of episodes, confirming the development of airflow obstruction rather than restriction.

In summary, there is evidence of temporality in the TB-CAO association, adding weight to the argument for causality. It appears that lung-function changes may evolve over time in patients with tuberculosis. Restriction appears to predominate in the active phases of TB and may mask underlying airflow obstruction, the latter appearing as the former resolves with treatment.[55] Thereafter, CAO may progress over months or years, and further episodes of TB increase the decline in lung function.

2.9.3. Confounders

Several potential confounders need to be considered when evaluating the association between previous TB and CAO. A confounder is defined as a variable/factor that is both a cause of the disease/outcome under study, as well as being correlated (either positively or negatively) with the exposure of interest.[116] Two important confounders to consider in the TB-CAO association are cigarette smoking and HIV status.

Cigarette smoking fulfills the criteria as a confounder in the causal pathway between TB and CAO. A number of systematic reviews have confirmed a positive association. The pooled odds ratios for association have been estimated at 1.7-2.2 for TB infection; 2.0-2.6 for TB disease; and 1.3-2.2 for TB mortality.[117–119] In a local Cape Town study of 2 401 adults, den Boon *et al* found a positive association between smoking and a positive tuberculin skin test (TST). An odds ratio of 1.99 (95% CI 1.62-2.45) was observed for ever-smokers having a positive TST, compared with never

smokers.[120] Groenewald *et al* estimated that 24% of pulmonary TB in South Africa could be attributed to cigarette smoking; 32% for men and 8% for women.[40] More strikingly, Sitas *et al* have attributed 56% of deaths to TB among South African Coloured men to cigarette smoking, with the attributable fraction being 36% for White men and 14% for African men. Attributable fractions among South African women were: 43% for Coloured women, 12% for White women and 4% for African women.[42] Cigarette smoke has been shown to impair alveolar macrophage function, by impairing cytokine responses and mycobacterial containment.[121] However, despite the potential for cigarette smoking to confound, the strong positive association between TB and CAO persists, even after adjusting for smoking.[18,25,26]

HIV infection is another potential confounder in the association between TB and CAO. There is increasing recognition of HIV as a cause of CAO/COPD (i.e. associated with the outcome).[122–125] Several mechanisms for the development of airflow limitation in HIV infection have been proposed, but this topic is beyond the scope of the present review.[125,126] Additionally, the well-known positive association between the immune-deficient state of HIV and TB satisfies the requirement for potential confounding.[21]

The magnitude of this confounding in the TB-CAO association is not known, as none of the larger epidemiological studies mentioned above have adjusted for HIV status, since most were conducted in low-HIV-prevalence countries. However, two studies conducted in South African miners found no differences in lung function loss between HIV-positive and HIV-negative subjects following TB,[127,128] suggesting that the association between tuberculosis and CAO is independent of HIV status (i.e. no confounding effect). This will need to be confirmed in future studies.

2.9.4. Reverse causation with smoking and tuberculosis

It is possible that the presence of COPD may place individuals at greater risk of the development of PTB (i.e. reverse causation), with COPD being the primary event. Potential reasons and mechanisms for this occurring are unconvincing. Possibilities are that impaired lung immunity in COPD may

predispose to the development of PTB. This could include the effects of COPD treatment (e.g. corticosteroids). Lee *et al*, examining a nationwide Taiwanese database of 1 000 000 beneficiaries, reported COPD to be an independent risk factor for the development of TB [HR 2.47, 95% CI 2.21-2.76].[129] There was evidence of an association between oral corticosteroid and oral β-agonists use and the development of PTB, but no association was found for inhaled corticosteroids. The retrospective database study design limits interpretation of these findings, and alternative hypotheses should be considered. However, Shu *et al*, in another retrospective Taiwanese study, confirmed these findings. There was an association in COPD between PTB and oral corticosteroid use and with high-dose inhaled corticosteroid use, but not with medium or low doses.[130] However, potential selection bias and the small numbers of subjects with TB equally limit interpretation of this study. Thus, although reverse causation is a possible explanation, given the data on the temporal relationship between PTB and CAO, it is unlikely that this mechanism plays a major role.

2.10. Mechanisms of airflow obstruction

In contrast to smoking-related COPD, the mechanisms responsible for chronic airflow limitation associated with previous TB have not been well studied.

2.10.1. Mechanisms of CAO in COPD

The CAO in COPD results from a combination of both obstructive bronchiolitis (small airways disease) and emphysema (parenchymal disease) - the relative proportion of each varying from patient to patient,[22,60] which develops over years or even decades of exposure to a causative agent, usually smoking.

Small airways, defined as those of less than 2 mm in internal diameter (fourth to fourteen generations), are the predominant site of airflow

obstruction. They have less cartilage than larger airways, a larger proportion of smooth muscle and fewer goblet cells. In normal lungs, these airways contribute little to airflow resistance, but in obstructive diseases of the lung (e.g. asthma and COPD) they become the major site of obstruction, because even minor changes in diameter result in large increases in airflow resistance.[131] In COPD, increased wall thickness results from a combination of inflammation, fibrosis and mucus plugging, which narrows the lumenal diameter. Mucous gland metaplasia results in hypersecretion of mucus, which, combined with impaired mucociliary clearance caused by squamous metaplasia, leads to plugging of airways. In addition, the increased mucus viscosity influences surface tension, which results in premature airway collapse during expiration.[81,131]

Airway wall volume, mucus metaplasia and plugging of small airways are positively associated with severity and progression of COPD.[132,81] Recently, McDonough *et al* assessed the small airways of 78 patients using multidetector CT scanning and MicroCT scanning. They were able to show a significant reduction in the number of airways measuring 2.0-2.5 mm for all GOLD stages of disease. Additionally, they showed a reduction in both the number and total cross-sectional area of terminal bronchioles in patients with GOLD stage 4 disease, which suggests that small airways narrow and disappear before the onset of emphysema, and accounts for the large increase in small airway resistance.[133]

The relationship between pathology in large and small airways is unclear. Hogg *et al* proposed that inflammation of the central and peripheral airways occurs independently of each other.[134] In support of this, the inflammatory profile is different in airways of differing caliber. However, the presence of bronchiectasis in larger airways is now recognised in patients with COPD and occurs in up to 57% of COPD patients, and relates to both and increased risk of exacerbations and mortality.

The presence of radiological emphysema is associated with both lower health status and increased mortality in patients. In emphysema, loss of elastic recoil associated with the parenchymal destruction results in the

premature closure of the airways on expiration. Interestingly, there is additional loss of both terminal bronchiole number and area (described above) in both centrilobular and panlobular emphysema.[133]

The chronic exposure to cigarette smoke, and other toxic gases and particles evokes both the early innate defense system (including the mucociliary escalator and epithelial barrier) and later adaptive immune response (with both humoral and cellular elements), with persisting chronic inflammation and attempts to repair and restore the tissue to its initial state.[134]

The lungs of smokers have consistently shown increased inflammatory cells as well as denuded epithelium,[60] with clusters of pigmented alveolar macrophages causing a characteristic respiratory bronchiolitis.[135] Macrophages, being five to ten times more numerous in subjects with COPD, appear to play a central role; being both activated and localised to areas of damage, as well as responsible for the recruitment of other immune cells.[60] The airways of patients with COPD additionally show increased numbers of neutrophils as well as lymphocytes - predominantly CD8 and B cell subtypes[134] - which are organised into lymphoid follicles and correlate with the degree of airflow obstruction.[131,134]

Airway inflammation in COPD is considered to be a Th1-type response, with high levels of IL-1, IL-6 and IFN-γ. Th17 cells, which induce the production of IL-6 from bronchial epithelial cells, stimulate mucin secretion (including both MUC5A and MUC5B). Increased levels of IL-6 and IL-17 have both been associated with increased risk of bronchial infections, exacerbations and hospitalisations.[81]

Destruction of the lung parenchyma appears to be facilitated through the release of multiple proteinases and matrix metalloproteinases (MMPs) by both neutrophils and macrophages,[136] with the resultant degradation of elastin (by neutrophil elastase) and increased excretion of desmosine (an elastin breakdown product). Patients with emphysema exhibit increased levels of MMP-1 (collagenase), MMP-2 and MMP-9 (gelatinase B).[60,137]

The action of proteolytic enzymes is normally balanced by the action of antiproteases (e.g. alpha-1-antitrysin, airway-epithelium-derived secretory leukoprotease inhibitor, and tissue inhibitors of matrix metalloproteinases - TIMPs). It is thought that cigarette smoke increases the production of proteolytic enzymes while decreasing the available antiproteases, tipping the protease-antiprotease balance in favour of tissue destruction. Genetic polymorphisms of various genes may account for the variable expression of disease in smokers.[60]

Patients with COPD display a greater intensity pro-inflammatory state compared to non-smokers, with increased NF-κB and decreased HDAC2 expression.[131] Smoking-induced oxidative stress may play a role in activating NF-κB, in turn increasing levels of TNF-α, IL-8 and other pro-inflammatory factors.[138] Additionally, surfactant protein-D (SP-D), a part of the innate immune system elevated in smokers, is associated with airway inflammation and may prove useful as a future biomarker.[65]

Large and small airways demonstrate differences in inflammation, with large airways exhibiting more macrophages and small airways more CD8 lymphocytes and neutrophils. Additionally, NF-κB expression is greater in the large airways, while HDAC2 expression is reduced in the small airways.[131]

The increased inflammatory reaction to cigarette smoke occurs before the detection of structural changes in the lung, or clinically detectable airflow obstruction.[135,139] The inflammatory reaction initiated by cigarette smoke appears to be independent of smoking intensity and continues long after smoking cessation. The mechanism of the ongoing inflammation in the lung after smoking cessation is unexplained, and various authors have hypothesised about the persistence of either auto-antigens or micro-organisms as perpetuating factors.[22,131]

2.10.2. Airflow obstruction associated with tuberculosis

2.10.2.1. Hypothesis of bronchial tree involvement

Endobronchial involvement in active pulmonary TB has been confirmed on CT scans and appears as centrilobular nodules, branching linear structures, ('tree-in-bud' appearance) or poorly defined nodules, being present in almost all cases of active TB.[140] Lesions in and around the small airways are the most characteristic feature of active TB, occurring in 95.0% of individuals. Although most lesions disappear by five months,[141] the resultant peribronchial fibrosis may cause fixed airflow obstruction.

Bronchiectasis, defined as abnormal permanent dilation of bronchi, is common after PTB and is another recognised cause of CAO. The association between TB and bronchiectasis was first noted in 1819 by Laennec, and later confirmed in post-mortem studies.[142] It is proposed that post-tuberculous bronchiectasis may result from endobronchial or peribronchial fibrosis, or stenosis leading to distal airway dilatation. Additionally, enlarged tuberculous or reactive lymph nodes may lead to atelectasis and post-obstructive bronchiectasis in lung distal to the glands. Furthermore, bronchi may become distorted and dilated in areas of parenchymal fibrosis and scarring, or following rupture of tuberculous glands into airways.[54] CAO in bronchiectasis correlates both with extent of disease and bronchial wall thickness, but the mechanisms responsible are unclear. Bronchospasm, retention of secretions, and intrinsic narrowing of small- and medium-sized airways resulting in gas trapping may be involved.[142]

Lesions in or surrounding small airways (<2 mm) may result in airflow obstruction in post-tuberculous lungs. These airways are not easily visualised radiographically, even with CT scans, but their involvement is inferred from the presence of gas trapping on expiratory CT scans and may take the form of complete closure (obliterative bronchiolitis) or cicatricial narrowing. Gothi *et al*, reported a strong correlation between a mosaic pattern of gas trapping and a previous history of tuberculosis,[143] while Long *et al* demonstrated the persistence of mosaic pattern attenuation after tuberculosis treatment, despite resolution of endobronchial and parenchymal changes.[140]

There is limited and conflicting evidence on the development and role of bronchial hyper-responsiveness after PTB.[53]

2.10.2.2. Hypothesis of inflammatory parenchymal destruction

Another potential mechanism for CAO after PTB is that lung parenchyma undergoes destruction during the active phase of disease, similar to that seen in smoking-related emphysema. Parenchymal destruction may increase pulmonary compliance, resulting in dynamic airway collapse with gas trapping.[26,142] Additionally, inflammation may persist long after treatment completion, resulting in ongoing chronic parenchymal destruction similar to that observed in smoking-related COPD. This mechanism is supported by similarities in the inflammatory profile observed in these conditions, with elevated levels of MMPs (specifically MMP-1 and MMP-9) in airways.[144] In a recent study by Tang *et al*, levels of cytokines (IL-6, TNFα, IFNγ and sIL-2R) were elevated in both conditions compared with controls, while subjects with comorbid TB and COPD had higher levels of sIL-2R, IL-6 and TNFα than subjects with either TB or COPD alone. This evidence may suggest that the persisting airway inflammation after active PTB may lead to COPD, and secondly supports the additive inflammatory and destructive potential when both infection and smoking-related COPD are established, and possibly when smoking continues after an episode of PTB.[145]

Tumour necrosis factor alpha (TNFα) is a central cytokine in the host's defense against TB. In certain Taiwanese populations, polymorphisms of the TNFα promoter region results in increased TNFα production and a 10-fold increase in COPD.[60.146] It is thus possible that persistently elevated levels of TNFα during and following PTB contribute to the development of changes similar to those observed in COPD.

However, emphysema is not a usual feature in PTB. Long *et al* found no convincing CT scan evidence of emphysema in patients with active tuberculosis.[140] In one small study, no reduction in DL_{CO}, considered a useful marker of emphysema, was found in patients with post-tuberculosis airflow obstruction (n=11).[147] Consistent with this, Martin *et al* found no evidence of

histological emphysema in a series of autopsies of subjects with acute TB and airflow obstruction.[148] Thus, the mechanism of CAO following an episode of TB requires further study.

2.11. Burden of Obstructive Lung Disease (BOLD) study methodology

The population-based study of Jithoo *et al* provided one of the most accurate estimates of COPD, and current and past PTB in a South African community. The major strength of this study was the use of standardised international methodology (the BOLD methodology) for the survey, which included spirometry using standard spirometers, trained technologists, and central quality control for all tests. Patients found to have COPD according to BOLD criteria form the basis for the studies reported in the present study. First, however, it is relevant to provide details of the BOLD methodology.

2.11.1. BOLD population selection and sampling

The BOLD methodology requires sites to recruit a minimum population-sample of 600 adults (300 men and 300 women). Subjects must be 40 years of age or older, non-institutionalised and living in an area with a total population of greater than 150 000 people. Sampling plans must be pre-approved by the Operations Centre.[14] For the Cape Town study (2005), the predominantly low-income urban areas of Ravensmead and Uitsig were chosen, with a population at the time of 36 334. These communities were known to have a higher prevalence of smoking, TB and, possibly, asthma than any other area in the country. This study followed on from a previous study, the Lung Health Study (LHS), carried out in the same community in 2002 by Jithoo *et al*. The LHS 2002 was a cross-sectional study comprising a 15% random sample of addresses (833 addresses), and recruiting persons >15 years old. The BOLD 2005 study sampled the same 833 addresses, but only recruited adults >40 years old. The BOLD Operations Centre approved this sampling methodology.[29]

2.11.2. BOLD definition of COPD

The BOLD methodology bases COPD diagnosis strictly on lung function criteria without requiring documented exposure to risk factors, or the presence of symptoms. Chronic airflow limitation is defined as a post-bronchodilator FEV1:FVC <0.7.[5,14] The NHANES III prediction equations for Caucasians are used to categorise severity, again using GOLD staging mentioned above. The limitations of these definitions have been presented on page 4 above.

2.11.3. BOLD spirometry

Lung function data in BOLD was performed in participants' homes using a portable spirometer: the EasyOne ndd Spirometer (ndd Medical Technologies, Andover, MA, USA).[14] Prior to its adoption by BOLD, the performance of this spirometer was evaluated in the large PLATINO study, which made use of 70 such spirometers every day for between three and six months. The spirometers were calibrated daily with a three-litre calibration syringe and investigators found good calibration stability, which was maintained for the duration of the study. Almost all calibration checks were within the ± 90 mL (3%) required by the American Thoracic Society (ATS) standards, and most were within ± 50 mL. During the survey, they found one defective calibration syringe and one spirometer had a faulty memory.[149]

Before and 15 minutes after an inhalation of a rapid-onset $beta_2$-agonist bronchodilator (200 µg of salbutamol), lung function was performed by certified technologists. All lung function data were assessed for acceptability and reproducibility in accordance with the ATS and European Respiratory Society (ERS) standards, and was performed centrally at the BOLD Pulmonary Function Reading Center (PFRC). Data not meeting these standards were excluded from analysis.[14] A review of the 9 893 spirometry tests in 14 countries during the BOLD study revealed that quality goals were

met in about 90% (i.e. FEV1 and FVC repeatable within 150 mL), thus confirming the reliability of the spirometer.[150]

2.11.4. BOLD questionnaire

The BOLD investigators developed questionnaires that included questions about respiratory symptoms, exposure to risk factors, health status and health utilisation. The questionnaires were administered in person by trained staff in the subject's native language. Although some of the questionnaires were based on standardised instruments, there do not appear to be reports of the precision, accuracy and repeatability of the questionnaires used in the BOLD study.[14,24]

Similar to other studies, the BOLD methodology based the assessment of previous TB status on responses to questions in the questionnaire only. For obvious reasons, more accurate methods like reports of microbiology, clinical records or radiology were not employed.[17] It is likely, however, that reliance on questionnaires to assess TB exposure results in an underestimation of previous TB, particularly in a high-prevalence setting. This fact was illustrated by Lam *et al* in a large population survey conducted in China (n=8 066), in which diagnosis of previous TB by questionnaire provided 232 cases and by chest X-ray, 1 954 cases.[26] This disparity might be explained in part by concerns about stigmatisation if participants report previous TB. This is likely to vary in different cultures; thus, these findings should not be extrapolated to other communities.

2.11.5. BOLD diagnostic reliability

As with any definition or test, basing the diagnosis of COPD on spirometric criteria alone has shortcomings. Firstly, a number of other conditions, such as chronic asthma and bronchiectasis, can result in irreversible airflow obstruction and may be misdiagnosed as COPD in these prevalence studies.[38] This question, and its likely impact on the reported results of BOLD studies that have now been performed in more than 30 sites globally, has not

been adequately addressed. Nor has an estimatation of the magnitude of this problem or possible correction factors that might improve the accuracy of the estimate of COPD when employing the BOLD criteria been proposed. In follow-up studies performed five and nine years after the first PLATINO Study in Latin America (which used methodology similar to that of BOLD Study), the prevalence of COPD remained relatively stable with only a small increase of 0.9% in Montevideo (five-year follow-up), and 0.4% in both Santiago de Chile (six-year follow-up) and Sao Paolo (nine-year follow-up).[151] However, the authors did not attempt to assess the accuracy of the diagnosis, and, in particular, the proportion that might have had asthma and other diagnoses.

Therefore, an important component of the present study is an attempt to assess the diagnostic accuracy of the BOLD methodology in diagnosing COPD.

2.12. Radiological tools for correlating lung structural abnormalities with function

Because radiology will be extensively utilised in the assessment of structural lung changes, a review of these techniques, in the context of the present study, is presented.

2.12.1. Radiological changes of tuberculosis

Radiological changes of active primary TB normally appear as homogeneous consolidation (usually segmental or lobar, but multifocal in 12%-24%), while nodular, linear, patchy and mass-like lesions have also been described.[152] In contrast, post-primary disease is characterised by parenchymal opacities, occurring predominantly in the apical and posterior segments of the upper lobes (83%-85%) and the superior segments of the lower lobes (11%-14%); the majority involve more than one segment, while cavitation occurs in 40%-45% of cases.[152,153] The parenchymal opacities are frequently heterogeneous and may be associated with nodular or linear lesions initially radiating from

the hilum, progressing to distortion of the bronchovascular and mediastinal structures. Tuberculomas, defined as round or oval, sharply marginated lesions, of 0.5-4.0 cm in diameter, may be either solitary or multiple, and are the predominant lesion in 3%-6% of post-primary disease.[152]

Bronchogenic spread of TB is observed in approximately 20% of chest X-rays and is identified as multiple nodules (5.0-10.0 mm) in a segmental distribution, frequently in a dependent (lower) region of the lung, distal to a cavity.[152] CT scanning, a far more sensitive tool, detects bronchogenic spread in 95% of TB cases. Centrilobular nodules (2.0-4.0 mm) form early in the disease, with bronchiolar caseous material being visualised as branching linear structures – the so-called 'tree-in-bud' pattern. Larger, ill-defined nodules (5.0-8.0 mm) are also observed, which appear to partially resolve into 'centrilobular nodules' with treatment. The larger nodules consist of outer, ill-defined areas of non-specific inflammation, while the smaller centrilobular nodules consist of dense caseous necrosis,[141] the majority of which disappear after treatment with minimal residual changes.[154] Cavitation starts as 3.0-4.0 mm lesions, centering on the centrilobular bronchioles, which enlarge and coalesce to form larger air spaces and resolve with residual scarring damage.[154]

Im *et al* have claimed that fibrosis and emphysema invariably result from bronchogenic spread of areas of caseation, with traction by adjacent scar tissue (so-called 'cicitricial emphysema') as well as bronchiolar stricture, being proposed as possible mechanisms for the emphysema.[154] Other investigators have not been able to confirm these findings.[140]

Radiographic areas of mosaic low-attenuation, thought to represent either gas trapping secondary to bronchiolar occlusion, or hypoperfusion secondary to arteriolar occlusion or vasoconstriction, have been demonstrated in active PTB. Im *et al*, using a similar pig model of disease, concluded that gas trapping was the more likely explanation and was unable to demonstrate a vascular contribution to the mosaic pattern.[154]

Other radiological findings that may occur in active TB include: bronchial wall thickening, lobular consolidation, interlobular septal thickening and pleural involvement.

The residual radiological abnormalities found after active PTB are varied. Upper-lobe changes are most common, and comprise atelectatic and fibrotic areas, as well as emphysematous bullae, bronchiectasis and calcified nodules. The trachea and large airways may show dilation and distortion secondary to pulmonary fibrosis. Volume loss is common, as is residual pleural and diaphragmatic abnormalities, and the presence of a pleural cap.[154,155]

Several methods have been described that assess for the presence of active TB on chest X-ray, as well as quantify the burden of disease. These methods vary from 'expert reader' opinion to semi-quantitative methods of assessment.[57,155,156] One such method, The Chest Radiograph Reading and Recording System (CRRS), employs a semi-quantitative method for assessing the common abnormalities of acute TB and their distribution, showing a good kappa statistic between readers (k=0.63, 95%CI 0.52-0.73).[157]

In contrast, there are no well-described or validated methods for documenting the presence of, or quantifying the burden of, previous pulmonary TB on either chest X-ray or CT scan. Described methods are non-standardised and non-quantitative, based largely on subjective descriptions by expert readers.[26,155,158]

2.12.2. Quantitative CT scanning in COPD

2.12.2.1. Technical aspects

Computed tomography (CT) images are captured in two-dimensional pixels, which when combined with the thickness of the tomogram slice (z-axis) is termed a voxel. A high-resolution (HRCT) protocol to visualise lung parenchyma involves axial slices 1.0-2.0 mm in thickness, spaced 10.0-15.0 mm apart, and reconstructed, traditionally performed using single-slice

scanners. Modern multi-detector scanners contain from 4 to 320 detectors, and are able to generate true volumetric data from contiguous slices 0.5-1.0 mm apart in a single breath hold, thus improving image resolution with reduced exposure times.[159] Image density is expressed as Hounsfield units (HU) and is visually displayed using a gray scale. Human tissue varies from –1 000 HU (density of air) to approximately +1 000 HU (density of cortical bone), with the density of water being 0 HU and blood being 40 HU.[160] The total radiation dose during CT scanning is a combination of the tube current (in mA), total exposure time and maximum voltage (kVp). Current lung imaging methods used in clinical research involve exposures of 1.0-3.0 millisievert (mSv) per scan, compared with 5.0-8.0 mSv per scan for standard protocols, which is similar or lower than an expected natural background radiation dose for an individual per annum (3.0 mSv).[160,161]

Images can be acquired at total lung capacity (TLC), functional residual capacity (FRC) or residual volume (RV), which yield different densities for lung parenchyma due to differences in aeration. Inability to perform full inspiratory/expiratory manoeuvres, adequately breath hold, or lie still (resulting in movement artifact) affect image capture. The use of concomitant spirometry (through the use of a volume controller), or careful coaching of subjects prior to scanning, may be used to ensure optimal lung volumes; the former being more precise, while the later is more practical. Use of the shortest possible scan time increases the probability of an adequate breath-hold, thus minimising movement artifact. This is achieved by using a fast gantry rotation time, the maximum number of channels available and the highest pitch.[160,162]

Insufficient radiation dose can result in excessive ‘noise’ on acquired images, resulting in error in density analysis. The ‘signal-to-noise’ ratio can be improved by increasing the radiation dose administered; however, the need for attaining meaningful attenuation values needs to be balanced with the risks of exposing subjects to increased radiation doses. However, an insufficient radiation dose results in excessive ‘noise’ on acquired images, leading to error in density analysis. Regular calibration against a

manufacturer-supplied 'phantom' is required to ensure both accuracy and precision. Varying CT slice thickness can introduce variation into density measurements (see below).[162,160,161]

2.12.2.2. Assessment of emphysema

Pulmonary emphysema is histologically defined as the permanent dilation of air spaces distal to the terminal bronchiole, with destruction of the intervening airspace walls. Emphysema is visualised on CT scan as low attenuation areas (LAA); however, the measurement of such LAA and the thresholds density cut-off that should be used to define radiological emphysema has been much debated.[163,164] Initially, a lung parenchymal density threshold of –910 HU or less was proposed using a single-slice scanner and 10.0 mm thick slices. This threshold correlates well with histological emphysema in resected lung tissue.[165] Subsequently, using HCRT protocols (1.0 mm slices), Gevenois *et al* reported that a threshold of –950 HU or less showed the strongest correlation with pathology specimens.[166] More recently, Madani *et al* found that the extent of emphysema was estimated best by using thresholds of –960 HU or –970 HU when using multi-detector CT (MDCT) protocols.[167] With automated quantitative techniques, the extent of emphysema is usually expressed at a percentage of lung parenchyma with low attenuation areas (e.g. %LAA –950 for the –950 HU cut-off). Normal lung parenchyma has a density of approximately –850 HU. It is important to remember that although %LAA correlates moderately well with histological emphysema, it is not specific, as other pathology may also yield low attenuation readings (e.g. cavities).[168,163] Currently, the <–950 HU threshold is most-widely used.[168]

As emphysema is not uniformly distributed throughout the lungs, most current computational software provides estimates of %LAA on either a zonal (upper, middle and lower zones) or a lobar basis.[163,164] Recently, Castaldi *et al*, using the large COPDGene cohort, used algorithms to estimate proportions of various radiological phenotypes of emphysema (centilobular, panlobular and pleural-based emphysema), and were able to show better correlation with physiological parameters using these methods.[169]

An alternative approach for detecting and quantitating emphysema is percentile densitometry, which provides a mean density value for the lung at a defined centile. This method may be preferable for longitudinal evaluation of emphysema, as it is less affected by changes in lung volume, but is less reproducible than the threshold method (i.e. density <–950 HU). Both the first and fifteenth percentile have been proposed; the former percentile shows better histological correlation when using MDCT, while the latter appears more robust if image artifact is present, and is more frequently quoted in current literature.[164,162,168,170]

Important sources of variation in measurement of %LAA exist. First, sub-maximal inspiration results in under-aeration of lung, which falsely increases parenchymal density measurement. Although these differences in density measures are marginal at 100% and 90% of TLC, differences became significant at lower levels of inspiration (e.g. 80%, 70% and 50% of TLC).[168,171] Additionally, CT slice thickness influences estimates of %LAA; thinner slices demonstrate a greater extent of emphysema. Thicker slices, although giving better resolution, have been made obsolete with the advent of MDCT protocols. Furthermore, a low signal-to-noise ratio also results in increased %LAA, although the mean parenchymal density is little affected.[162] Interestingly, recent smoking cessation has been shown to increase the %LAA,[172] which is thought to result from rapid clearing of soot, tar and, possibly, inflammation upon cessation, revealing underlying low-attenuation areas.[162,168] Despite these limitations, quantitative assessments of emphysema are more reproducible than visual assessments performed by experienced radiologists.[173] Barr *et al*, in the COPDGene workshop, demonstrated inter-reader agreement on manual quantification in COPD to be moderate to poor, while the concordance between visual and quantitative measures was 75% for emphysema.[174] Furthermore, radiologists tend to underestimate disease extent in less-severe emphysema, and overestimate disease in more-severe disease.[168]

2.12.2.3. Assessment of airways

A number of techniques have been developed to measure and assess airway anatomy in COPD, with a number of parameters being measured. Focus has traditionally been on airway remodelling, and in particular, thickening – which is often expressed as a percentage of bronchial wall area.[160] Initially, methods of airway quantification used manual tracing methods to assess single or a few predominantly large airways.[175] With the advent of MDCT, manual methods were replaced by automated techniques. Most common among these is the 'full-width-at-half-maximum' (FWHM) technique. This method is performed by placing a point at the bronchial lumen centre, with software calculating the CT attenuation values along lines radiating outwards from this point. In this way, airway wall boundaries are defined at the point where attenuation is halfway to the maximum on the lumen side, and halfway to the minimum on the parenchymal side.[176] Other parameters can then be calculated: airway wall thickness (AWT); luminal area; wall area percentage; and airway perimeters. However, the FWHM method is known to systematically overestimate airway wall thickness, and underestimate luminal area. This overestimation increases as airway size decreases.[177,162,159,178] To improve accuracy, a number of different quantitative algorithms have been developed, examples of these include: maximum-likelihood algorithms on the grey level; ellipse fitting to the lumen; and score-guided erosion algorithm methods. Currently, there is no consensus on a 'gold-standard' for this method.[176,177]

Multiplanar reconstruction using MDCT data permits the tracing of airway diameter down to the segmental and sub-segmental levels. The software algorithms are designed to extract airway centerlines through these reconstructions, then re-sample images perpendicular to the airway direction at intervals equally spaced along the airway.[179] These measurements may be used in summary measures of bronchial wall area. For example, Pi10, which is the square root of the wall area of a hypothetical bronchus with an internal perimeter of 10.0 mm; this measure is a calculated value obtained from linear

regression models, using data obtained from all measured bronchi within an individual.[179,168]

There are a number of sources of variation in quantitative assessment of airways. Foremost among these is the algorithm used, as values obtained from the algorithm are not merely density measures, but rather require the division and interpretation of voxels into 'airway lumen' and 'surrounding tissue'. Detection and measurement of the airway lumen is relatively simple because of the high degree of density contrast between the intraluminal air and surrounding tissue. More complicated is the outer delineation of the airway wall, especially when the surrounding lung parenchyma or bronchovascular bundle density is similar to that of the airway wall.[162] Thus, it is important that the same algorithm be used for all subjects within a study, while comparisons of values obtained by different algorithms should be discouraged.

In addition to the algorithm used, airway caliber and resolution of the CT scan may affect airway assessment. Small airways have been shown to have a higher error rate in measurement compared with larger airways (as discussed above). This has resulted in investigators frequently focusing primarily on the analysis of larger airways. Over time, the ever-increasing scanner resolution will improve airway assessment. Additionally, biological factors such as lung volume may affect assessment, with larger lung volumes being shown to result in larger airway lumen diameter.[162]

Small airways (<2.0 mm in diameter) are of particular interest in COPD, as they are the most important sites of airflow obstruction. However, they are normally below the resolution of CT scan detection, unless their walls become thickened due to inflammation or filled with exudates. Detection of these airways is limited by the resolution of the scanner (i.e. the size of the voxel), which is normally 0.5 mm, and reliable airway measurements have only been consistently demonstrated down to an airway diameter of 2.0 mm.[180,159,131] However, indirect evidence of small airway dysfunction is the presence of gas trapping on expiratory CT scans. Gas trapping is defined as a 'less than normal increase in lung attenuation and lack of volume reduction

after expiration'.[164] On expiration, normal lung density increases, thus, areas of lung where gas trapping is present appear less dense than the surrounding lung, which provides useful information on lung structure below the resolution of CT images. Quantification of gas trapping on expiratory scans in COPD is relatively new, and a threshold of <–856 HU on expiration has been proposed. The value –856 HU is derived from a conversion of 6.0 mL/g of lung inflation on inspiration (i.e. approximately normal lung density on inspiration). Expiration manoeuvres to both RV and FRC have been used to determine gas trapping, and optimal respiratory manoeuvres have not yet been defined.[168,164,160,162]

The interpretation of radiological findings of gas trapping is difficult due to the lack of a pathological reference for comparison. Furthermore, in COPD, quantitative measurement of gas trapping is complicated by the need to separate areas of true gas trapping from residual air in emphysematous areas. Several different techniques have been proposed to overcome this, with some authors using 'voxel-by-voxel ventilation maps', which calculate the change in density of voxels between inspiration and expiration.[168] Glaban *et al* used this approach and defined voxels with a density <–950 HU on inspiration to have 'emphysema', while those with a density of >–950 HU on inspiration but <–856 HU on expiration were considered to have 'functional gas trapping'.[181] Despite the lack of a pathological 'gold-standard' comparator, CT measures of gas trapping have been shown to correlate well with physiological measures of airflow obstruction (e.g. FEV1:FVC).[168,182]

An alternative measure of gas trapping is the expiratory:inspiratory mean lung density ratio (E/I ratio). This ratio, which is not yet widely adopted, compares the mean lung density at FRC (expiration) to the mean lung density at TLC (full inspiration), and has been proposed as a potentially better measure than the –856 HU threshold mentioned above, as it demonstrates better ROC curves compared with other measures.[160,176]

2.12.2.4. Correlation between imaging and lung function and other clinical features

Quantitative CT measurements of both emphysema (%LAA) and airway wall thickness (AWT) correlate with lung function measures. Nakano *et al* demonstrated correlation between AWT (using FWHM methods) and peak expiratory flow rate (PEFR), percentage predicted FVC and RV:TLC ratio, but not FEV1:FVC or diffusion capacity.[183] Washko *et al*, in a cohort of 224 subjects, found that airway wall attenuation added additional information and was independently associated with FEV1.[184] Nakano *et al* reported that in COPD, radiological assessment of intermediate-airway wall area correlated well with histological measurement of small-airway wall area, suggesting that intermediate-sized airway wall assessment could be used as a surrogate measure for small-airway pathology.[185] However, Hasegawa *et al* demonstrated that correlation of AWT with percentage predicted FEV1 improved as airway caliber declined.[186] Dijkstra *et al* found AWT to be a better predictor of FEV1 than the emphysema component; however, combined emphysema scores and AWT only predicted 40.0% of the variance in percentage-predicted FEV1. These authors suggested that obtaining values on expiration may be better predictors of FEV1 than those performed at TLC.[179] Other authors have been unable to show a relationship between airway dimensions and FEV1.[187] Coxson *et al* and others postulated that poor resolution of the all-important small airways may be responsible for the relative insensitivity of CT scanning to predict changes in FEV1.[180,186] In support of this theory, a remarkable correlation has been shown between measures of gas trapping and spirometry (FEV1:FVC and predicted FEV1 percentage),[182] as well as with residual volume.[131] Some authors reported that measures of gas trapping (i.e. %LAA –856) have a stronger association than measures of emphysema (i.e. %LAA –950), with both FEV1 and FEV1:FVC.[188]

Radiological measures of emphysema have been associated with both lung function and lung function decline. Mohamed Hoesein *et al* showed in a cohort of 2 085 men, an association between extent of emphysema and both a lower FEV1 and a greater decline in FEV1 on follow-up.[189] Castaldi *et al*

showed that patterns of emphysema were more predictive of FEV1, dyspnoea scores and six-minute walk distance, than %LAA –950. Pleural-based and panlobular emphysema patterns were found to have a larger impact on physiological measures than centrilobular patterns.[169]

In terms of symptomatology, Grydeland *et al* found that both %LAA and Pi10 were independently associated with dyspnoea in COPD, while Pi10 was additionally associated with both cough and wheezing.[190] Other authors have confirmed these findings, demonstrating the association of AWT with respiratory symptoms (dyspnoea, wheezing and bronchitic symptoms).[179,187] Han *et al* reported that AWT and severity of emphysema were independently associated with exacerbation frequency; furthermore, that in subjects with low levels of emphysema, AWT exerted greater influence than the emphysema component. Interestingly, these authors found AWT, not wall area percentage, was predictive of exacerbation frequency, and postulated that airway wall percentage area may mask underlying airway wall thickening and pathology when bronchi are dilated.[178] In terms of mortality, the Norwegian GenKOLS study found CT measures of emphysema to be a strong independent predictor of mortality, where subjects having moderate-to-severe emphysema scores had a 19-month shorter survival than other subjects. Airway wall thickness did not independently predict mortality, but demonstrated a positive additive interaction in the presence of emphysema.[191]

These observations provide support for further use of CT scans to phenotype patients with COPD. Classifying COPD as either airway-predominant or emphysema-predominant disease may, in future, allow more focused research and guide selection of therapies.[192]

2.12.3. Emphysema estimates from other cohorts

Emphysema is a histological diagnosis and is common in the general population, occurring in 30%-50% of cigarette smokers, 8% of cigar smokers and 3% of never-smokers at post-mortem. Pathological subtypes are: centrilobular, with loss of the respiratory bronchioles; panlobular, with

uniform destruction of the secondary lobule; and paraseptal emphysema, characterised by multiple peripheral bullae or septae.[193]

Recently, the large MESA Lung/SHARe Study population-based cohort study, used quantitative CT to assess 7 914 adults subjects. They found that the percentage of emphysema (at a threshold of –950 HU) varied from 2.2% (in African Americans) to 3.6% (in Whites).[193]

In a different study of 463 COPD patients matched with controls, Grydeland *et al* demonstrated the median %LAA –950 to be 8.9% in male COPD cases, and 4.7% in females, while the corresponding median values in the control group were 0.7% and 0.3%, respectively.[194] The %LAA increased with the number of pack-years smoked.

In another study, conducted among 1 140 male lung-cancer screening participants, Mets *et al* reported median quantified emphysema of 0.8% (IQR: 0.4%-1.5%) and median air-trapping values of 0.8% (0.8%-0.9%) for the whole population, while the average Pi10 was 2.4 ± 0.5 mm. A total of 437 participants (38%) had COPD on lung function testing. Using a diagnostic model, comprising: emphysema scores; air-trapping scores; body mass index (BMI); pack-years; and smoking status, they were able to identify 274 of these 437 participants as having COPD, with 85 false positives. This equated to a sensitivity of 63% (95% CI 58%-67%) and a specificity of 88% (95% CI 85%-90%), with a PPV of 76% (95% CI 72%-81%) and NPV of 79% (95% CI 76%-82%).[195,196]

As part of the COPDGene cohort, 4 062 subjects had CT scans and spirometry. Of these, 2 145 (53%) had COPD on spirometry (GOLD stage 1 or higher), and 1 917 (47%) served as smoking controls. In this study, quantitative CT measurements correlated well with spirometry. The mean %LAA –950 (sd) on inspiratory CT scans was: 2.5% (2.8) for controls; 6.0% (6.0) for GOLD stage 1 COPD; 8.4% (8.6) for GOLD stage 2 COPD; 18.2% (12.7) for GOLD stage 3 COPD; and 28.1% (14.0) for GOLD stage 4 COPD. Mean measurements of gas trapping on expiratory scans (%LAA –856) were: 11.7% (9.6) for controls; 20.6% (12.0) for GOLD stage 1 COPD; 28.9% (15.2) for GOLD stage 2 COPD; 48.2% (16.9) for GOLD stage 3 COPD; and 63.3%

(12.8) for GOLD stage 4 COPD. The Pi10 (sd) was reported as: 3.6 mm (0.1) for controls; 3.6 mm (0.1) for GOLD stage 1 COPD; 3.7 mm (0.1) for GOLD stage 2 COPD; 3.7 mm (0.1) for GOLD stage 3 COPD; and 3.8 mm (0.1) for GOLD stage 4 COPD. The corresponding AWT at the fourth generation airways (in mm) was: 5.5 mm (0.7) for controls; 5.4 mm (0.7) for GOLD stage 1 COPD; 5.0 mm (0.6) for GOLD stage 2 COPD; 4.9 mm (0.6) for GOLD stage 3 COPD; and 4.8 mm (0.6) for GOLD stage 4 COPD. Regional differences in early small-airways disease were seen, with disease being predominant, in upper lobes in mild and moderate COPD (GOLD stage 1 and 2). Regional differences were not prominent in severe COPD (GOLD stage 4 disease).[188]

Using a retrospective cohort of 1 272 adults with chronic airflow obstruction, Kurashima *et al* used visual CT assessment to show that 40.6% (517) of subjects had COPD with emphysema, while 8.2% (104) had COPD without emphysema, 14.0% (178) had asthma with emphysema, 13.3% (169) had asthma without emphysema, 10.0% (128) had other respiratory disease with emphysema, and 13.8% (176) had other respiratory disease without emphysema. CT-diagnosed emphysema was associated with increased mortality in both asthma and COPD patients.[197]

The pattern of emphysema appears to vary according to overall burden of disease. Subjects with lower %LAA (<10%) have more mild centrilobular disease, whereas higher %LAA (>10%) is associated with more panlobular and pleural-based emphysema, as well as moderate- and severe-centrilobular disease.[169] Using visual assessment of emphysema pattern, investigators of the Multi-Ethnic Study of Atherosclerosis (MESA) study assessed CT scans from smokers with COPD and controls aged between 50-79 years, with >10 pack-years of smoking. Of the 318 included subjects, 113 (36%) showed the presence of emphysema (14% centrilobular predominant; 9% paraseptal predominant; and 4% panlobular predominant). Subjects with centrilobular or panlobular emphysema exhibited greater dyspnoea, reduced six-minute walk distance (6MWD), and a lower diffusion capacity. A total of 17% of smokers without COPD on spirometry had radiological evidence of emphysema.[198]

In summary, evidence of emphysema on CT scans appears to antedate detectable spirometric airflow obstruction in smokers, but detectable radiological changes (emphysema scores, airway measurements and gas trapping) do not fully account for observed airflow obstruction in all patients with COPD. The evidence to date suggests that small-airways disease initially develops in the upper lobes, and becomes more diffuse as the disease worsens. The centrilobular pattern of disease is more common in early COPD, while panlobular and paraseptal disease increases as the disease worsens.

In conclusion, CT scans provide a useful method for examining the extent and nature of emphysema, correlate with clinical features, and may be used as a component of assessments for COPD phenotyping. The relevance of phenotyping in treatment selection is currently under investigation. The sensitivity of the method makes it suitable for the evaluation of TB-associated airflow limitation, particularly for examining the extent and regional distribution of emphysema (in relation to post-TB lung scarring). However, problems of resolution might limit its usefulness for studying the site of disease in small airways, and disease in this location may have to be inferred from other measures.

Chapter 3. Hypothesis

The central hypothesis for this work is that chronic airflow obstruction in patients with a history of previous TB differs in terms of pathophysiology, natural history and responsiveness to treatment from patients without this risk factor for COPD. The three specific objectives are:

Objective 1 (main objective)

To compare cohorts of subjects with chronic airflow obstruction, with and without evidence of previous pulmonary TB, for differences in structural abnormalities, pathophysiology, natural history and response to treatment that might support considering patients with a past history of pulmonary TB as a distinct phenotype of COPD.

Objective 2

To examine the diagnostic performance and limitations of the Burden of Obstructive Lung Disease (BOLD) methodology as an estimate for the prevalence of COPD in communities.

Objective 3

To examine the natural history and predictors of mortality of COPD in a cohort of adults over 40 years of age identified using the BOLD methodology, in 2005, in an area with high-prevalence of TB.

Chapter 4. Methodology

This chapter describes the methodology utilised to meet the research objectives; it covers the study design, study population, inclusion and exclusion criteria, and discusses all tests performed and their sequence, and both the statistical and radiological analyses that were undertaken.

4.1. Study design

These specific objectives were addressed by studies performed on a cohort of subjects diagnosed with COPD in a community survey in 2005.

4.2. Study population

The study population comprised all subjects identified as having COPD in 2005 in a community-based previous prevalence study performed by researchers at the University of Cape Town Lung Institute, in collaboration with the Desmond Tutu TB Centre (Stellenbosch University), using the Burden of Obstructive Lung Disease (BOLD) methodology.

This study identified 196 people (101 females, 95 males) as having COPD (GOLD stage 1 or higher). Thirty-four people fulfilled spirometric criteria for GOLD stage 1, 109 for GOLD stage 2, 48 for GOLD stage 3, and 5 for GOLD stage 4.

4.3. Sampling methods and background to study population

The BOLD study enrolled subjects that had previously participated in the Lung Health Study 2002 (LHS2002); a burden of lung disease study performed by the same investigators.

4.3.1. Study site: description of the populations of Ravensmead and Uitsig

Ravensmead and Uitsig are two adjacent, predominantly low-income suburbs of Cape Town, which in 2001 had an estimated population of 36 334 living in 5 592 households. The estimated mean household income was R2 732 per month, and the number of persons per address ranged from 6.63 to 13.83 for flats, and 5.5 to 12.9 for houses. Only 36% of adults were employed in the formal sector, and 47% had an education level of less than Grade 7. The prevalence of smoking and alcohol use were high: 33% of men and 30% of women were defined as 'risky drinkers' (i.e. >4 drinks per day for men, and >3 drinks per day for women). Tuberculosis incidence was also high, estimated at 776/100 000, with 6% of new TB cases being HIV positive. The background HIV prevalence among local antenatal clinic attendees in 2001 was 7.9%. All homes in these areas were electrified, which limited biomass fuel exposure.[29]

4.3.2. Lung Health Study 2002: sampling methods and findings

The LHS2002 was a cross-sectional study comprising a 15% random sample of addresses (833 addresses). The adult population survey was conducted in persons >15 years of age. The sample design was a random cluster survey, with an address forming the sampling unit/cluster. If the household head did not consent to the survey, that dwelling was replaced by the house to the right, and, failing that, the house to the left of the originally selected residence. A sample size of 3 500 participants was required to meet power calculations.

The final sample comprised 3 483 adults, of whom 38.3% >40 years reported at least one respiratory symptom, and 18.2% Grade 2 or higher dyspnoea (scored using the modified MRC Dyspnoea Score). Symptomatic chronic bronchitis was reported in 7.2% of adults >15 years, 49.9% of participants were current smokers, and 7.6% were ex-smokers. A total of 9.7% of subjects reported a 'doctor-diagnosed' episode of TB, 7.0%

reported healthcare-worker (usually doctor) diagnosed asthma, and 5.5% reported emphysema.

4.3.3. BOLD 2005 study: sampling methods

The BOLD study used the original LHS2002 enumeration lists, and resampled all 833 addresses surveyed in that study. However, as required by the BOLD method, only adults >40 years were recruited. Approximately two thirds of the adults sampled had participated in the LHS2002. The remaining third were either LHS2002 non-responders or new residents at the selected addresses.

Of the 1 377 eligible persons, 958 consented (69.6%) to participate, and 419 declined (30.4%). All provided questionnaire data, and 896 attempted spirometry, with 62 being excluded on medical grounds. Spirometry of acceptable quality was obtained in 847 subjects (61.5% of 1 377). Spirometry data from 49 subjects was of poor quality and not analysable. The major findings of the BOLD 2005 study have been discussed in the Literature Review [see page 21].

4.4. Ethical approval

Ethical approval to conduct the current (2010) follow-up study was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town, the Stellenbosch University Ethics Committee, and the local health authority (the City of Cape Town). Participation was voluntary and informed written consent was obtained from all participants prior to enrolment. Information was provided and consent was obtained in each participant's preferred language. After appropriate counselling, consent for HIV testing was also obtained.

4.5. Inclusion/exclusion criteria

Inclusion criteria**:**

- Subjects diagnosed with COPD (GOLD stage 1 or higher) in the BOLD study in Ravensmead/Uitsig in 2005.
- Written informed consent to participate and willingness to undergo all test procedures.

Exclusion criteria:

- Subjects in the BOLD study that could not be traced.
- Subjects who did not consent to participate.
- Subjects who were unable to perform spirometry or had a contra-indication to bronchodilator testing including:
    - A myocardial infarct within the last three months.
    - A resting pulse rate of more than 120 beats/minute.
    - Cataract surgery, or a major surgical procedure in the last month.
    - Any other co-morbidity (e.g. unstable angina or pneumonia) that, in the judgment of the investigators, might affect the performance of the test or place the subject at risk.
    - Chest or abdominal surgery in the past three months.
- Pregnancy (of any gestational age).
- Respiratory tract infection with unresolved symptoms in the four weeks prior to the visit *(subjects with 'temporary exclusion criteria', e.g. recent surgery, could be rescheduled once recovered).*
- Active TB, on treatment or with symptoms requiring investigation.
- Subjects with known advanced or untreated malignancy.
- All HIV-positive subjects.

The rationale for excluding HIV-positive persons was the high probability for the presence of confounding factors in these subjects, for example: altered immune status and increased risk of respiratory and opportunistic infections.

The sample size was considered too small to adequately adjust for such confounders.

4.6. Examinations and study procedures

All subjects underwent all investigations, and were required to attend the University of Cape Town Lung Institute on three separate occasions. With the exception of chest CT scans, all tests were performed at the University of Cape Town Lung Institute (Mowbray, Cape Town). The CT scans were performed at Vincent Pallotti Hospital (Pinelands, Cape Town), a local, private (non-government) hospital.

4.6.1. Questionnaires

Study personnel were trained to administer the questionnaires in a standardised manner. The study co-ordinator performed quality control for both method of administration and completeness of data. Three questionnaires were administered in the follow-up study in 2010:

4.6.1.1. The BOLD Questionnaire

The first questionnaire administered was the BOLD Core Questionnaire that had previously been administered in 2005. This questionnaire records data on demographics, respiratory symptoms, risk factors and respiratory diagnoses [see Appendix 1 – BOLD Core Questionnaire]. Both English and Afrikaans versions were available to participants - the translation to Afrikaans had been performed by the Stellenbosch University Language Centre in preparation for the previous BOLD study and involved translation, back-translation and piloting in the vernacular of the test community.

4.6.1.2. Additional Tuberculosis Questionnaire

A second questionnaire was the Additional Tuberculosis Questionnaire (ATbQ), which was intended to gather more details of reported episodes of TB, including: their number and date; method of diagnosis; location of

treatment administration; hospitalisations; treatment duration; and resolution of symptoms following treatment completion [see Appendix 2 – Additional Tuberculosis Questionnaire].

4.6.1.3. St George's Respiratory Questionnaire

The St George's Respiratory Questionnaire (SGRQ) is a tool designed to measure impact of respiratory symptoms on overall health, daily life, and perceived wellbeing in subjects with fixed and reversible airway obstruction (i.e. COPD and asthma).[199] It is comprised of two parts: the first assesses symptoms and the second assesses activity and impact; these are combined to form a total score. The questionnaire was originally designed for self-administration; however, due to low levels of literacy in the study population, and to improve the consistency of the results, the questionnaire was administered by the study personnel to all participants, regardless of functional literacy [see Appendix 3 - St George's Respiratory Questionnaire] Permission to use the SGRQ was obtained prior to commencement of the study.

4.6.2. Lung physiology

Participant's weight and height were measured at the first visit. Height was recorded as the average of measurements, using a Stadiometer (Holtain Limited, Britain), which was calibrated daily with a 600 mm metal rod. Weight was measured on a standing scale (Seca™, Seca Ltd, United Kingdom), which was calibrated annually by the manufacturer. The following tests of lung physiology were also performed:

4.6.2.1. Spirometry

Spirometry was performed at all three visits as follows:

At Visit 1, spirometry was performed with the same ndd EasyOne™ Spirometer (ndd Medical Technologies, Andover, MA, USA) used in the BOLD study of 2005 [see p46].

At Visit 2, spirometry was performed using both the ndd EasyOne™ and an office-based spirometer – the nSpire Spirometer® (Ferraris™,

Columbia, USA). Both spirometers were calibrated daily using a three-litre syringe, and at least monthly with biological controls (staff at the Lung Institute).

At Visit 3, spirometry was performed using the nSpire Spirometer® (details above).

All spirometry was performed before and after administration of both a rapid-acting $beta_2$-agonist and an anti-cholinergic bronchodilator. First, ipratropium bromide anhydrous 80 µg (100 µl) (Atrovent manufactured by Boehringer Ingelheim™) was administered via a pressurised metered dose inhaler (pMDI), followed immediately by four puffs (100 µg each) of salbutamol via a pMDI device (Ventolin GlaxoSmithKline™). Spirometry was repeated after 45 minutes.

The following spirometric variables were measured: forced expiratory volume in 1 second (FEV1); forced vital capacity (FVC); FEV1:FVC ratio; and peak expiratory flow rate (PEFR).

Prior to Visit 2, all subjects were requested to withhold all respiratory medication (i.e. a wash-out period) as follows: theophylline and aminophylline-containing preparations for one week; long-acting $beta_2$-agonists and anti-cholinergics for 48 hours; and short-acting bronchodilators ($beta_2$-agonists and anti-cholinergics) for six hours prior to testing.

4.6.2.2. Diffusing capacity for carbon monoxide

The diffusing capacity for carbon monoxide (DL_{CO}) was performed at Visit 2 using VMAX 2130® (made by Sensormedics™, Yorba Linda, CA, USA), which was calibrated daily. The single breath method of DL_{CO} determination was used.

4.6.2.3. Whole body plethysmography

Whole body plethysmography was performed at Visit 3, to allow for comparison of lung volumes measured by this method and results of the CT scan. The Eagle & Bodybox Pulmonary System® (Ferraris™, Columbia, USA) was used and calibrated daily with a three-litre syringe, and at least monthly with biological controls. The following variables were measured: functional

residual capacity (FRC); vital capacity (VC); total lung capacity (TLC); inspiratory capacity (IC); vital capacity (VC); residual volume (RV); and RV:TLC ratio.

4.6.2.4. Reference equations

As in the BOLD survey of 2005, the NHANES III prediction equations for Caucasians [see Table 1] were used: Lower Limit of Normal (LLN) values use the lower fifth Percentile, or –1.645* Standard Error of Estimate.

Table 1: NHANES III prediction equations for Caucasians.

	Intercept	Age	Age^2	$Height\ (Pred)^2$	$Height\ (LLN)^2$	Intercept (LLN)	R^2
White Males >20 yr							
FEV1	0.5536	–0.01303	–0.000172	0.00014098	0.00011607		0.8510
FVC	–0.1933	0.00064	–0.000269	0.00018642	0.00015695		0.8668
FEV1:FVC	87.340	–0.2066				78.372	0.1538
White Females >18 yr							
FEV1	0.4333	–0.00361	–0.000194	0.00011496	0.00009283		0.7494
FVC	–0.3560	0.01870	–0.000382	0.00014815	0.00012198		0.7344
FEV1:FVC	90.809	–0.2125				81.015	0.3955
Reference: Hankinson et al AJRCCM 199;159:179-197							

Because there are no NHANES III reference equations for static lung volumes obtained by plethysmography, the European Community of Coal and Steel (ECCS) reference equations were used[200] in chapters where analysis of plethysmography is reported.

4.6.3. Assessment of responses to systemic glucocorticosteroids and a long-acting $beta_2$-agonists

At Visit 2, after a washout period, all subjects were given a therapeutic trial of oral glucocorticosteroids and a long-acting $beta_2$-agonist (LABA) for a minimum of two but not more than four weeks (beginning at Visit 2 and ending at Visit 3). The treatment comprised prednisone tablets in a dose of 20 mg per day and formoterol 24 mcg twice daily administered via a pMDI. Subjects were instructed and coached in the use of a pMDI to ensure optimal

delivery of the inhaled formoterol. At Visit 3, spirometry was repeated at least 12 hours after the last (evening) dose of formoterol.

Participants with the following conditions were not administered glucocorticosteroids: uncontrolled diabetes, peptic ulcer disease or any condition that, in the view of the investigators, might place the subject at risk of a serious adverse event from oral corticosteroid use. Similarly, the LABA was not administered to subjects at risk of side effects (e.g. tachyarrthymias).

To monitor adherence, subjects were asked to return all unused prednisone tablets, and a pill count was performed. No adherence tests were applied to inhaler use.

4.6.4. Skin prick allergy testing

Skin prick tests were performed at Visit 1, to establish the presence and nature of allergies, on subjects with any of the following risk factors: reversibility on spirometry (i.e. an increase of FEV1 of ≥12.0% and ≥200 mL after administration of bronchodilator); a family history of atopy; or symptoms suggestive of asthma or allergic rhinitis/hay fever [see Appendix 4 – Atopic Questionnaire].

Trained personnel, using allergens supplied by Lab Spec™ (Randburg, South Africa) performed the skin prick testing. The following were tested: negative control (diluent); positive control (Histamine 10 mg/mL); mould mix; cat dander; house dust mite (HDM) (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*); grass mix; and Bermuda grass.

4.6.5. Chest imaging

Lung imaging comprised of chest X-rays and high-resolution CT scans.

4.6.5.1. Chest X-ray

Chest X-rays were performed at Visit 2, at the University of Cape Town Lung Institute, using the Odelca DR chest radiology apparatus (Delft Imaging Systems, The Netherlands). Posterior-anterior (PA) views were obtained on all subjects and were reported independently by two pulmonologists

experienced in chest radiology. A further description of the reporting methods and analysis is provided on page 130.

4.6.5.2. CT scanning of chest

A high-resolution CT scan of the chest (HRCT) without contrast medium was performed on all subjects at Visit 3. Images were captured at full inspiration and full expiration.

CT images were obtained by a single experienced radiographer using a standardised image acquisition protocol. The same 64-channel Siemens Sensation 64 Multidetector scanner (Munich, Germany) was used for all studies. The tube current was 140 kVp and 40-60 mAs (effective), and beam collimation was a minimum of 64 x 0.6 mm. Images were reconstructed using a smooth kernel, which were standardised following baseline phantom evaluations, thus giving similar noise characteristics across all scans. Subjects were examined in the supine position, and CT scans were performed from the apex to the base of the lungs during breath-holding at full suspended inspiration (i.e. TLC) for the inspiratory scans, and full expiration (i.e. RV) for expiratory scans. Breath-holding at both lung volumes was rehearsed with each subject prior to the CT examination to ensure minimal respiratory motion during scanning. The scanning procedure required approximately 15-20 minutes of the scanner time. Full details of the scanning procedure, scanner techniques and breath-holding manoeuvres are in Appendix 5 – TOPD image acquisition protocol.

Quantitative analysis of the scans was performed at the Department of Radiology, David Geffen School of Medicine, University of California Los Angeles, USA by Dr Jonathan Goldin and his colleagues. The CT scan images were transferred electronically to Los Angeles after removal of all information that might reveal participants' clinical identity or clinical status, and analysis was performed using MedQIA software (Los Angeles, CA, USA). Similarly, assessment of bronchial anatomy was performed in a blinded manner by collaborators at Radboud University Medical Center, Nijmegen, Netherlands, using software previously developed for this purpose.

The following quantitative parameters were calculated:

On Inspiratory CT scans:

- Lung and lobar volumes
- Total lung and lobar densities
- Percentage low attenuation areas <–950 HU (emphysema score)
- Percentage area attenuation <200 HU (fibrosis score).

On expiratory scans:

- Total lung and lobar densities
- Percentage low attenuation areas <–860 HU (gas trapping score).

Bronchial anatomy:

- Pi10.

The cut-point of –860 HU was chosen as the measure of gas trapping after discussion with the collaborators in UCLA. This measure is almost identical to the more traditional –856 HU cut-point, and the 4 HU difference between the two definitions is within the scanner limits of resolution and repeatability, and, thus, unlikely to influence findings [see page 54].

4.6.6. Blood tests

Finger prick blood specimens were obtained from each subject for:

4.6.6.1. HIV testing

At Visit 1, subjects were counselled by an experienced Voluntary Testing Counsellor or physician, and were tested for HIV status after obtaining full written consent. The protocol required that HIV-positive subjects be provided with post-test counselling, immediate referral to the nearest appropriate HIV treatment centre, but they were to be excluded from the study.

4.6.6.2. Blood glucose

As a safety precaution, a random blood glucose test was performed at Visit 2, prior to commencement of the trial of prednisone; subjects with elevated levels were not administered prednisone.

4.6.7. Schedule of study visits

Initial Contact

The Community Health Workers employed by the Desmond Tutu TB Centre traced subjects in the community, and the purpose and details of the study were explained to all potential participants. If subjects agreed to participate, they were provided with a date to attend for Visit 1. All visits took place at the University of Cape Town Lung Institute. See Figure 1 below.

Visit 1

At Visit 1, the following were performed:

1. Written consent was obtained.
2. HIV consent and counselling, bedsides HIV-ELISA testing followed by post-test counselling.
3. BOLD questionnaire.
4. The Additional Tuberculosis Questionnaire.
5. The St George's Respiratory Questionnaire
6. Physical Examination.
7. Spirometry (pre and post bronchodilator) using the ndd EasyOne™ spirometer.
8. Allergy tests.

Visit 2

At Visit 2, the following were performed:

1. MRC dyspnoea score.
2. Pre and post bronchodilator spirometry using:
   - The ndd EasyOne™ spirometer
   - The nSpire spirometer®.
3. Diffusing capacity for carbon monoxide (DL_{CO}).
4. Chest X-ray.
5. Blood sugar testing (finger prick).
6. Education and administration of medication for corticosteroid and bronchodilator trial.

Visit 3

At Visit 3 the following were performed:

1. MRC dyspnoea score.
2. Repeat spirometry (pre and post bronchodilator) using the nSpire spirometer.
3. Whole body plethysmography.
4. Subjects were transported to Vincent Pallotti Hospital (Pinelands, Cape Town), for an HRCT scan.

Where necessary, subjects were transported back to the UCT Lung Institute for follow-up and referral for management of any identified medical problems.

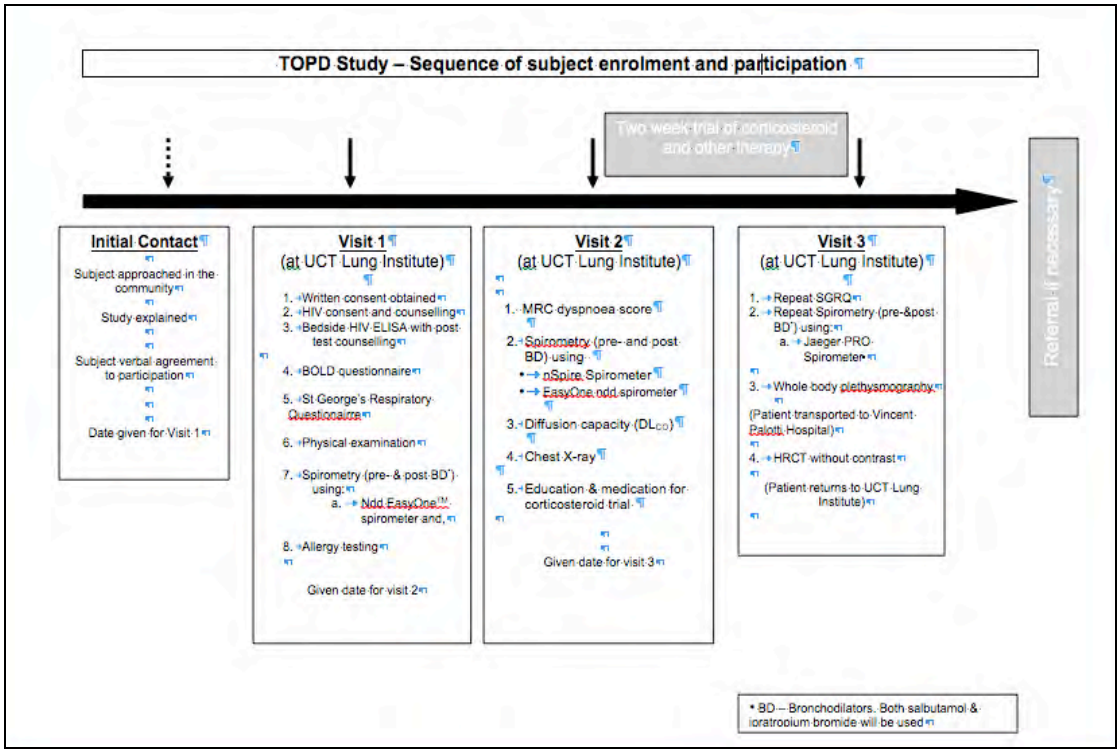

Figure 1: Schedule of visits and procedures.

Rationale for visit schedule

The repeated Easyone ndd spirometry (pre- and post-bronchodilator) on Visits 1 and 2, allowed opportunity to assess both the impact of respiratory medication withdrawal on lung physiology, and the repeatability of spirometry performed with this spirometer in subjects not using medication. Pairing of

the two different spirometers at Visit 2 allowed direct comparison of the two instruments against each other. Whole body plethysmography was performed at Visit 3, to compare values of lung volumes obtained with the plethysmography with those based on quantitative CT scan imaging at the same Visit. Whole body plethysmography was not additionally performed at Visit 2, for reasons of cost and practicality, diffusing capacity for carbon monoxide (DL_{CO}) was performed at Visit 2 for logistical reasons, Due to the chronic nature of the disease, changes in DL_{CO} at Visit 3 was not anticipated.

4.7. Determination of cause of death

For subjects reported as having died since the 2005 BOLD study, attempts were made to determine the causes of death. This involved questioning the nearest living relatives or suitable alternatives. Additionally, two data bases/death registers (the South African Medical Research Council and the City of Cape Town databases) were scrutinised for information on causes of death. Searches involved using name, surname and date of birth to confirm identities. Identity numbers were not available and could thus not be used.

4.8. Subject transport and remuneration

Since many participants were of advanced age and in relatively poor health, transportation for each visit to the Lung Institute and the Vincent Pallotti Hospital was provided in Lung Institute vehicles. In accordance with UCT Faculty of Health Sciences Human Research Ethics Committee guidelines, subjects were provided with R40.00 per visit for expenses relating to their attendance. Visits lasted between three and four hours. When participants used their own or public transport, they were reimbursed with R120.00 per visit.

4.9. Data management

All completed questionnaires, data forms and reports were printed, dated and signed by the team member concerned, and placed in each subject's research folder. Data capturers performed double-entry data capture, and data was entered onto databases, without personal subject information to ensure subject anonymity. A unique subject study number was used to identify subjects. On completion of the data capture, the raw data was data-locked.

4.10. Statistical methods

Grouping of study population by previous tuberculosis status

The study population was divided into three groups: subjects without any evidence of previous pulmonary TB (no previous TB or NPTB group); subjects with definite evidence of previous pulmonary TB (definite previous TB or DPTB group); and subjects with some evidence for previous pulmonary TB (probable previous TB or PrPTB group). The latter two groups were combined to form the previous TB (PPTB) group.

Because the correct classification of subjects into the above groups was pivotal to the study hypothesis, a separate chapter is devoted to this classification [see Chapter 7].

Once categorised, the two groups, NPTB and PPTB, were compared by univariate analysis, comprising Student's t-tests and Wilcoxon tests for continuous variables, and Chi-squared tests for categorical data. Thereafter, three-way comparisons were made between the groups: NPTB, DPTB and PrPTB. Univariate analysis comprised Analysis of Variance and Kruskal-Wallis Test for continuous variables, and Chi-squared tests for categorical data.

Multivariate analysis was performed for variables found to be significantly different between the groups, adjusting for potential confounders. Linear and logistic regression modelling was performed using

forward, backward and stepwise model building, where appropriate. Inclusion and exclusion confidence thresholds are included in the appropriate text.

Analysis of predictors of mortality was performed using original data from the initial BOLD study (2005), with univariate and multivariate analysis being performed in a similar manner to the above.

To assess the accuracy of the BOLD methodology, the results obtained with the same questionnaire and spirometer used in the BOLD 2005 survey were compared with those obtained in 2010. Additionally, results from the handheld spirometer (EasyOne ndd) were compared at sequential visits, as well as to office-based spirometry. Where relevant, correlation coefficients and Bland-Altman analysis were performed. Statistical analysis was performed using the statistical software package Stata version 12 (Statacorp, Texas, USA).

4.11. Patient safety, benefits and harms

No serious risk to the subjects was anticipated. With the exception of finger-prick blood sampling and allergy skin prick testing, the investigations were non- or minimally invasive, and the lung function testing and CT scans involved minor discomfort.

Risks associated with the trial of treatment using oral glucocorticosteroids was reduced by using only half the 40 mg dose of prednisone recommended in the South African Thoracic Society Guidelines[4] (20 mg was administered). Concerns were the possibility of reactivation of latent TB infection, and increased susceptibility to community-acquired and opportunistic infections. Subjects were assessed for adverse effects of treatment at the relevant visits.

The CT scans and chest X-rays exposed the subjects to radiation; however, the total amount of radiation each subject received from the CT scans was equivalent to that of background radiation from living in Cape Town for 18 months (estimated at between 5-8 mSv per subject). To reduce

risks, additional scans following contrast were not performed. The dose of radiation from the chest X-ray (0.1 mSv) is approximately 1/100th the radiation dose of a CT scan, and is equivalent to living in Cape Town for 12 days. Pregnant women were excluded from the study.

Benefits to the subjects for participation in the present study were the review of their lung disease (and co-morbidities), with referral for appropriate further investigation and management, as well as optimisation of treatment for their obstructive lung disease.

4.12. Funding

This study was investigator-initiated and funded by the host institution – the University of Cape Town Lung Institute, and supported by three research scholarships awarded to the lead investigator:

- AstraZeneca/South African Thoracic Society Respiratory Research Fellowship (2009)
- South African Medical Research Council (MRC) Grant for Self-initiated Research (2010)
- Discovery Foundation Academic Fellowship Award (2011)
- MRC PhD Scholarship – National Health Scholars Programme – 2013.

Chapter 5. Results of Follow-up of the BOLD 2005 Cohort: Overview of Demographic and Clinical Characteristics, Death and Spirometry Changes

5.1. Introduction

This chapter describes the results of the follow-up study of subjects identified as having COPD in the BOLD 2005 survey, including their subsequent clinical course, and predictors of mortality (Objective 3 page 62)

5.2. The BOLD 2005 cohort

The BOLD 2005 study included 847 subjects with analysable spirometry results. Of these, 196 subjects (23.1%) had evidence of airflow obstruction defined as FEV1:FVC <0.7, and 651 (76.9%) did not. Of the former, 34 (4.0%) were in GOLD stage 1 disease; 109 (12.9%) in GOLD stage 2; 48 (5.7%) GOLD stage 3, and 5 (0.6%) GOLD stage 4 disease.

5.3. The BOLD 2010 Follow-up study enrollment

Repeated attempts to contact all 196 subjects to request their participation in the Follow-up study yielded the following [see Figure 2]: 19 subjects (9.7%) declined participation, 11 subjects (5.6%) had moved from the community/area and were uncontactable, and 45 subjects (23.0%) had died. A further 14 subjects (7.1%) were excluded on various grounds: 13 (6.6%) on medical grounds such as dementia (5); substance abuse (alcoholism and/or drug addiction (3); bronchial carcinoma (2); carcinoma of larynx (1); heart disease (1); and 'collapsed lung' (1). One subject was excluded after study

completion, as he was enrolled in error (having the same name and address as the intended subject). The correct subject was later confirmed to have been alive at the time of the Follow-up study, but died shortly after at the age of 93.

One hundred and seven subjects (54.6%) participated in the study, but three withdrew after Visit 1, and one was unable to perform acceptable spirometry. Therefore, analysable lung function was obtained in 103 (52.6%) subjects, and 104 (53.1%) underwent chest imaging (chest X-ray and CT scan).

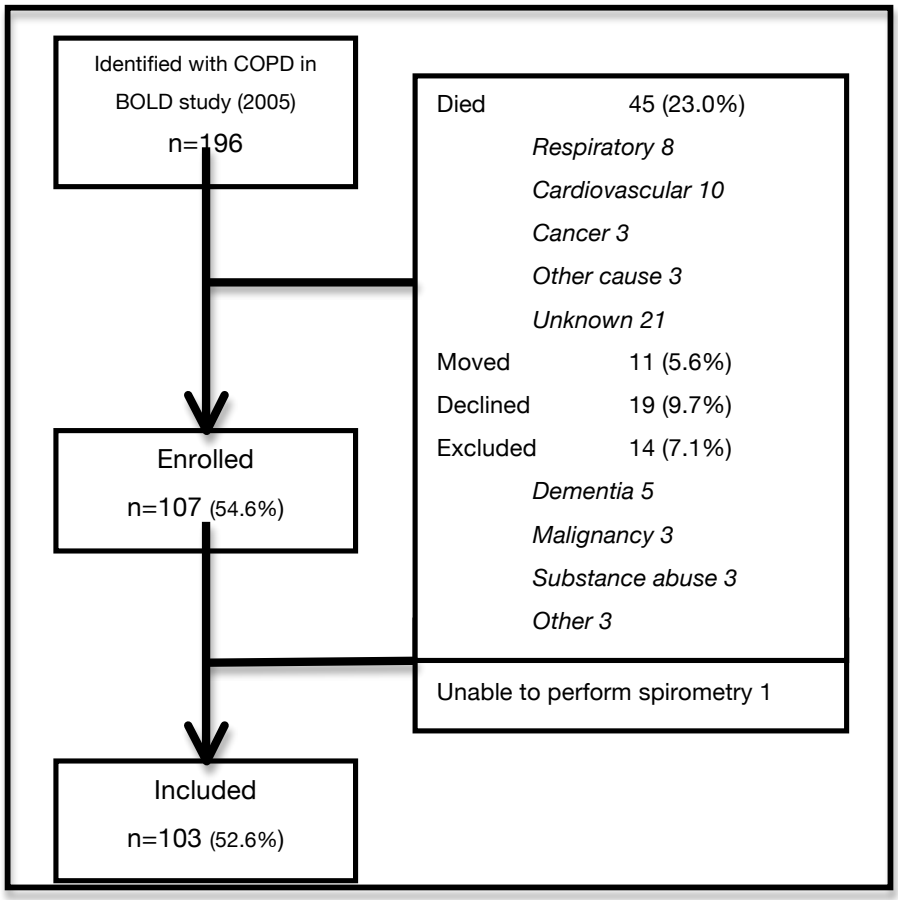

Figure 2: Disposition of subjects in the BOLD 2005 Follow-up study.

5.4. Mortality in BOLD 2005 cohort

In 2005, the mean age of all subjects identified with COPD was 59.0 years (sd=10.9, range 40.8-92.5 years). The mean age of the 45 subjects who died was 63.3 years (sd=11.2, range 41.1-91.6 years); 24 were men (53.3%) and

21 women (46.7%). Of the original cohort, 25.3% of the men (24 of 95) and 20.8% of the women (21 of 101) had died. Of the subjects that died: 6 (13.3%) had been classified in 2005 as GOLD stage 1; 20 (44.4%) as GOLD stage 2; 15 (33.3%) as GOLD stage 3; and 4 (8.9%) as GOLD stage 4. Thus, between 2005 and 2010: 17.7% (6 of 34) of GOLD stage 1 had died; 18.3% (20 of 109) of GOLD stage 2 had died; 31.3% (15 of 48) of GOLD stage 3 had died; and 80.0% (4 of 5) of GOLD stage 4 had died [see Figure 3].

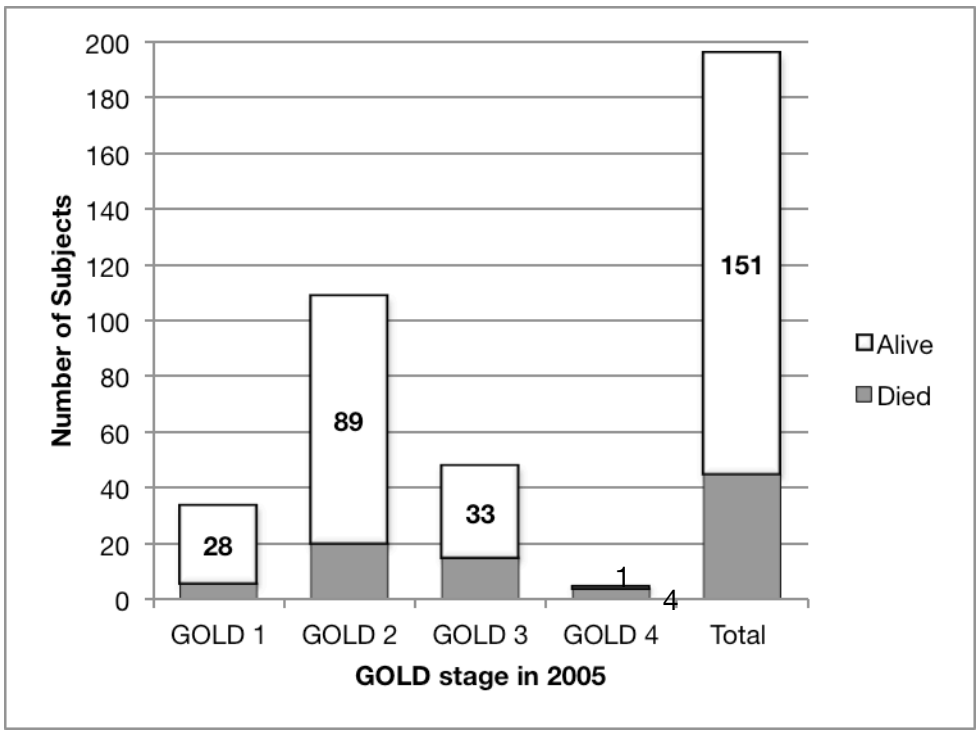

Figure 3: Mortality by GOLD stage in 2005.

5.4.1. Causes of mortality

Suspected cause of death was determined, based of analysis of two death registry databases (the South African Medical Research Council and the City of Cape Town databases) [see page 76]. **Table 2** shows the suspected causes of death.

Table 2: Suspected cause of death in BOLD 2005 subjects.

Cause	Number (%)	
Respiratory Cause	8 (17.8%)	
COPD		5 (11.1%)
Respiratory Disease		1 (2.2%)
Asthma		2 (4.4%)
Malignancy	3 (6.7%)	
Colon Carcinoma		2 (4.4%)
Metastatic Liver Cancer		1 (2.2%)
Cardiovascular	10 (22.2%)	
Heart Failure		4 (8.9%)
Hypertension		2 (4.4%)
Myocardial Infarction		1 (2.2%)
Cerebrovascular accident		3 (6.7%)
Other	3 (6.7%)	
Renal Failure		1 (2.2%)
Septicaemia		1 (2.2%)
Alcohol abuse		1 (2.2%)
Unknown / Uncertain	21 (46.7%)	
Total	45 (100.0%)	

5.4.2. Risk factors for mortality in the BOLD 2005 cohort

5.4.2.1. Univariate analysis

The univariate analysis of associations with mortality included the following independent variables: age; gender; smoking status; smoking burden; GOLD stage of COPD in 2005; history of previous TB; pipe/cigar smoking; dusty job; heart disease; hypertension; diabetes; and years of schooling. Results are shown in Table 3.

Table 3: Univariate analysis of risk factors for mortality.

	Alive		**Died**		***p-value***	***Test***
Total	151		45			
Age						
Mean	57.8		63.3			
Median	57.5		63.4		*0.0033*	*Wilcoxon*
Min	40.8		41.1			
Max	92.5		91.6			
IQR	49.3 - 65.1		55.4 - 70.7			
Male	71	47.0%	24	53%		
Female	80	53.0%	21	47%	*0.457*	*Chi2*
Smoking						
Never smoker	22	15%	5	11%		
Ever smoker	129	85%	40	89%	*0.588*	*Chi2*
Current	89		34			
Ex-smoker	40		6		*0.3445*	*Chi2 (trends)*
Smoking Burden						
Median pack-years	11.3		17.7			
(IQR)	(4.84 – 22)		(7.87 - 27.30)		*0.0575*	*Wilcoxon*
BOLD status 2005						
GOLD 1	28		6			
GOLD 2	89		20			
GOLD 3	33		15			
GOLD 4	1		4		*0.0062*	*Chi2 (trends)*
Tuberculosis						
Previous TB	50	33.1%	13	28.9%		
No Previous TB	101	66.9%	32	71.1%	*0.594*	*Chi2*
Pipe/Cigar smoking	30	20.1%	8	17.8%	*0.727*	*Chi2*
Dusty Job	90	59.6%	21	46.7%	*0.124*	*Chi2*
Heart Disease	9	6.0%	5	11.1%	*0.239*	*Chi2*
Hypertension	46	30.5%	17	37.8%	*0.356*	*Chi2*
Diabetes	13	8.6%	5	11.1%	*0.610*	*Chi2*
Years of Schooling	n=150		n=45			
Years	7		6			
IQR	6-8		3-8		*0.048*	*Wilcoxon*

On univariate analysis, only increasing age, GOLD stage in 2005, and years of schooling showed a significant association with mortality. Burden of smoking (i.e. number of pack-years) showed a trend towards a positive

association (Wilcoxon p=0.0575). The remaining independent variables showed no association with death.

5.4.2.2. Multivariate analysis

Multivariate analysis was performed using logistic regression, and included the following as variables: age; gender; burden of smoking; previous TB; GOLD stage in 2005; and years of schooling [see Table 4].

Table 4: Multivariate analysis of risk factors for mortality.

Variable	**OR**	***p-value***	**95% CI**
Age	1.05	*0.003*	1.02-1.09
Gender *(males as reference)*	0.64	*0.256*	0.29-1.38
GOLD 1	Ref	*Ref*	Ref
GOLD 2	1.11	*0.845*	0.38-3.29
GOLD 3	2.47	*0.140*	0.74-8.23
GOLD 4	29.16	*0.006*	2.61-325.22
Pack years	1.01	*0.332*	0.99-1.02
Years of schooling	0.90	*0.106*	0.80-1.02
Tuberculosis	1.92	*0.137*	0.81-4.58

In the multivariate analysis, only increasing age (p=0.003) and GOLD stage 4 disease (compared with GOLD stage 1 disease, p=0.006) showed a statistically significant association with mortality.

5.5. Follow-up cohort: demographics

Of the 107 subjects enrolled for Visit 1, 49 were men (45.8%) and 58 were women (54.2%). Three women withdrew and one man was unable to perform spirometry. The mean and median ages were 63.0 and 63.1 years, respectively (range 46.4-82.7 years, IQR 55.2-69.8 years) [see Figure 4 and Table 5]. All enrolled subjects described themselves as ‘coloured’ (i.e. mixed race).

Table 5: Age group ranges.

Age groups by decade	n	%
40 to 49	9	8.4%
50 to 59	38	35.5%
60 to 69	34	31.8%
70 to 79	21	19.6%
>80	5	4.7%
Total	**107**	**100.0%**

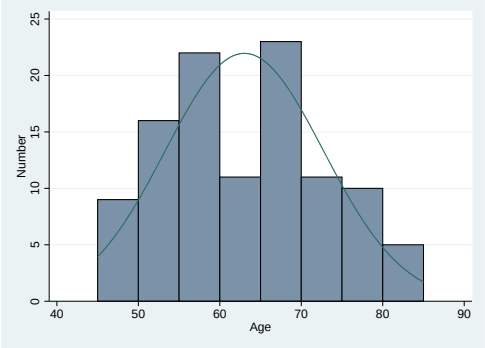

Figure 4: Age group distribution.

5.5.1. Smoking status

Smoking status was assessed with two questionnaires.

The standard BOLD Core Questionnaire, contained the following questions:

- Have you ever smoked cigarettes?
- How old were you when you first started regular cigarette smoking?
- How old were you when you last stopped?
- On average, over the entire time that you smoked, about how many cigarettes per day did you smoke?
- Have you ever smoked a pipe or cigar?
- Do you now smoke a pipe or cigar?

The Additional Smoking Questionnaire was developed to identify and quantify all forms of smoking, and captured variation in amount smoked at various stages of life [see Appendix 6 – Additional Smoking Questionnaire].

The results obtained with the BOLD (2010) and Additional Smoking Questionnaire (2010) are presented below [Table 6 and Table 7 respectively]:

Table 6: Smoking status: results obtained with the BOLD questionnaire (2010).

(n=107)	n	%	Pack Year (mean)	Pack Year (sd)	Pack Year (min)	Pack Year (max)
Never Smoked	13	12.2%	0	0	0	0
Ex-Smoker	34	31.8%	26.9	24.7	0.1	94
Current Smoker	60	56.1%	24.8	20.7	3.1	104

Table 7: Smoking status: results obtained with Additional Smoking Questionnaire (2010).

Cigarette smoking	**n**	**%**	**Pack Year (mean)**	**Pack Year (sd)**	**Pack Year (min)**	**Pack Year (max)**
Never	12	11.4%	-	-	-	-
Ex-smoker	38	36.2%	24.6	21.7	0.2	90.3
Current Smoker	55	52.4%	27.7	22.3	0.95	119
Cannabis smoking			**Joint Year[#] (mean)**	**Joint Year (sd)**	**Joint Year (min)**	**Joint Year (max)**
Never	74	70.5%	-	-	-	-
Ex-user	24	22.9%	62.6	82.6	0.3	310
Current-User	7	6.7%	457.5	600.6	2	1760
'Other' smoking			**Pipe[ξ]/Unit[ϕ] Year (mean)**	**Pipe/Unit Year (SD)**	**Pipe/Unit Year (Min)**	**Pipe/Unit Year (Max)**
Never	71	67.6%	-	-	-	-
Pipe	27	25.7%	151.63	236.9	0	1180
Methaqualone (Mandrax)	7	6.6%	116.4	132.2	3	379
Other (Opium x1, Tik i.e. Methylamphetamine x 1)	2	1.9%				

***Only 105 completed the Additional Smoking Questionnaire*
 # 'Joint Year' is defined as one joint per day, daily for 1 year.
ξ 'Pipe Year' is defined as one pipe per day, daily for 1 year
ϕ 'Unit Year' is defined as one pill, pipe or button per day, daily for 1 year

5.5.2. History of previous tuberculosis

Of the original 196 subjects from the BOLD study (2005), 63 (32.1%) reported a previous episode of TB. Previous TB status (PPTB) in the TOPD study was assessed in two different questionnaires:

- The BOLD questionnaire
- An Additional Tuberculosis Questionnaire [discussed in Chapter 4: Methodology – page 67].

5.5.2.1. Results obtained with the BOLD Questionnaire

At follow-up, 41 subjects (38.3%) reported one or more episodes of PPTB. One subject who reported PPTB in 2005 failed to report this in 2010, while

seven subjects who reported PPTB in 2010 did not report this in 2005 [see Table 8].

Table 8: Comparison of previous tuberculosis status using the BOLD questionnaires 2005 and 2010.

	TB status in 2010		
	PPTB	**No PPTB**	**Total**
TB status in 2005			
PPTB	34	1	35
No PPTB	7	65	72
Total	41	66	107

5.5.2.2. Results obtained with the Additional Tuberculosis Questionnaire

With the Additional Tuberculosis Questionnaire, 36.5% (n=39) reported PPTB, and 63.6% (n=68) of subjects had no PPTB [see Table 9].

Table 9: Previous tuberculosis status using the Additional TB Questionnaire.

	Number of episodes of PPTB					
	(0)	**(1)**	**(2)**	**(3)**	**Total**	%
No PPTB	68	-	-	-	68	63.6%
PPTB	-	26	12	1	39	36.5%

Significantly more men than women reported PPTB: 23 (46.9%) versus 16 (27.6%), respectively (Chi2: p=0.038). The median age of subjects with PPTB was 4.1 years younger than those without, but this difference was not statistically significant (Wilcoxon p=0.242) [see Table 10].

Table 10: Previous tuberculosis status by age.

	n	**Mean**	**Median**	**Min**	**Max**	**IQR**
No previous TB	68	63.8	63.9	46.4	82.7	55.4 - 71.5
Previous TB	39	61.6	59.8	47.9	81.9	53.1 -68.6
						(Wilcoxon: p=0.242)

The mean age of subjects' first episode of TB was 39.4 years (sd=16 years, range 6-77 years). One subject was unable to recall the year of their first

episode, and for the remainder, 20 subjects (52.6%) reported that their first episode occurred before the age of 40 years [see **Figure 5** and **Table 11**].

Table 11: Age of first episode of tuberculosis.

	n	%	Cum %
Age < 10	1	2.6%	2.6%
Age 10 -19	2	5.3%	7.9%
Age 20 -29	10	26.3%	34.2%
Age 30 - 39	7	18.4%	52.6%
Age 40 - 49	9	23.7%	76.3%
Age 50 - 59	5	13.2%	89.5%
Age 60 - 69	3	7.9%	97.4%
Age 70 - 79	1	2.6%	100.0%
Total	38		

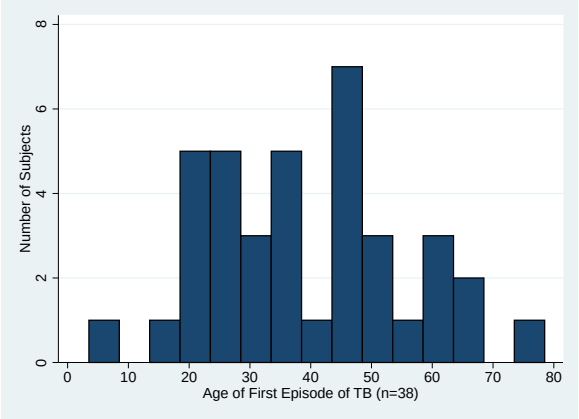

Figure 5: Age of first episode of tuberculosis.

The 39 positive responders suffered a total of 53 episodes of PPTB [details in Table 12]. Twenty-six subjects (66.7%) reported one episode of PPTB, 12 subjects (30.8%) reported two, and one subject (2.6%) reported three episodes of PPTB. A new episode of PPTB occurring subsequent to the BOLD study (2005) was reported in 10 subjects. Of these, seven occurred in 2005 (two retreatment cases, and five new cases), one in 2007 (new case) and two occurred in 2008 (one retreatment, one new case). One of these subjects reported two episodes of TB in 2005.

Table 12: Description of episodes of previous TB, using the Additional TB Questionnaire.

	Number				
Total number of subjects with Prev TB	39				
Total number of episodes of TB		53			
Hospitalisations for TB		9			
	n	**Mean (months)**	**sd**	**Min**	**Max**
1st Episode TB (n=39)					
Treatment duration unknown	7	-	-	-	-
Treatment duration known	32	6.25	1.74	2	12
2nd Episode (n=12)					
Treatment duration unknown	1	-	-	-	-
Treatment duration known	11	6.45	2.16	3	12
3rd Episode (n=1)					
Treatment duration unknown	1	-	-	-	-
Total TB treatment duration (n=39)					
Treatment duration “unknown”	7	-	-	-	-
Treatment duration known	32	8.47	3.78	2	18

5.5.3. HIV status

All subjects were tested for HIV at enrollment. HIV was an exclusion criterion for the study, but no subjects screened positive and, thus, no subjects were excluded on this basis.

5.5.4. Comorbidity

Of the 107 included subjects, 73 (68.2%) reported at least one comorbid condition, with hypertension (48.6%) and diabetes (12.1%) being the most common. Full details of comorbidities are presented in Table 13 below.

Table 13: Comorbid medical conditions.

(n=107)	**n**	**%**
No medical comorbidity	34	31.8%
Cardiovascular disease		
Hypertension	52	48.6%
Heart disease	15	14.0%
ASD repair	1	0.9%
High cholesterol	10	9.3%
Endocrine		
Diabetes	13	12.1%
Thyroid disease	1	0.9%
Arthritis	18	16.8%
CNS disease		
CVA	1	0.9%
Epilepsy	1	0.9%
Bell's Palsy	1	0.9%
Glaucoma	1	0.9%
Anxiety	2	1.9%
GIT disease		
GORD	1	0.9%
PUD	1	0.9%
Cancer	2	1.9%
Injury		
Head	1	0.9%
Spinal	1	0.9%
Motor Accident	1	0.9%
Allergic Rhinitis	2	1.9%
Skin		
Eczema	1	0.9%
Psoriasis	1	0.9%

5.5.5. Atopy Questionnaire: respiratory symptoms and atopic disease

A questionnaire on respiratory symptoms and atopic respiratory diseases was administered to all subjects [see Appendix 4 – Atopic Questionnaire]. The results are presented in Table 14. A total of 28.0% subjects (30 of 107) reported a physician-based diagnosis of asthma; 20.8% (22 of 106, with 1 no response) a personal history of asthma; 50.5% (n=54) periodic wheezing;

57.9% (n=62) a periodic cough; and 59.8% (n=64) periodic dyspnoea. Sixty seven percent of subjects (71 of 106, 1 no response) reported periodic cough, wheezing or dyspnoea in the last 12 months.

Ten percent (n=11) reported a physician diagnosis of allergic rhinitis, while 22.6% (24 of 106, 1 no response) reported a personal history of allergic rhinitis, and 33.6% (n=36) bouts of nasal blockage, rhinorrhea and sneezing not associated with common cold symptoms.

Table 14: Responses to administered Atopic Questionnaire.

	n	Positive responses	%
Asthma Diagnosis			
Diagnosed by physician	107	30	28.0%
Personal history	106	22	20.8%
Periodic wheezing	107	54	50.5%
Periodic cough	107	62	57.9%
Periodic dyspnoea	107	64	59.8%
Periodic symptoms in last 12 months	106	71	67.0%
Allergic Rhinitis			
Diagnosed by physician	107	11	10.3%
Personal history	106	24	22.6%
Bouts of Nasal Symptoms	107	36	33.6%

5.5.6. Skin prick allergy tests

Skin prick tests were performed on all subjects who responded positively to any question in the Atopic Questionnaire, or who demonstrated reversibility on lung function testing [discussed in the methodology on page 71]. On this basis, 93 of 107 (86.9%) subjects underwent skin prick tests. Positive results to antigen, defined as a wheal of 3 mm or greater in diameter, were obtained in 39.8% (37 of 93) of those tested, and one had an uninterpretable result [see Table 15 below]. Of the subjects with positive results, 25 (67.6%) were positive to *Dermatophagoides pteronyssinus* antigen, 27 (73.0%) were

positive to *Dermatophagoides farinae* antigen, 16 (43.2%) were positive to grass mix, 7 (18.9%) to each of mould and Bermuda grass, and 8 (21.6%) to cat antigen.

Table 15: Skin prick allergy test results.

(n=107)	**n**	**%**
Test results		
Negative	55	51.4%
Positive	37	34.6%
Not performed	14	13.1%
Un-interpretable	1	0.9%
Positive results (n=37)	**n**	**%**
House dust mite (*Dermatophagoides pteronyssinus*)	25	67.6%
House dust mite (*Dermatophagoides farinae*)	27	73.0%
Mould mix	7	18.9%
Cat	8	21.6%
Grass-mix	16	43.2%
Bermuda grass	7	18.9%

5.5.7. Health status: St George's Respiratory Questionnaire

Results with the SGRQ are presented in Table 16. One hundred and six of 107 subjects completed the SGRQ, but two failed to respond to all questions due to comorbid disease. The median values (and IQR) for the total, symptom, activity and impact domain scores were: 33.4 (IQR 14.1-54.1); 37.8 (IQR 14.1-59.5); 53.6 (IQR 29.3-73.2) and 19.1 (IQR 4.5-40.1) respectively [see Figure 6 and Table 16].

Table 16: St Georges Respiratory Questionnaire scores at Visit 1.

	n	Mean	Median	sd	Min	Max	IQR
Symptom score	106	38.06	37.81	25.35	0	83.38	14.07 - 59.53
Activity score	106	49.25	53.62	31.33	0	100	29.26 - 73.21
Impact score	104	24.67	19.05	23.38	0	99.28	4.45 - 40.12
Total score	104	34.73	33.4	24.35	0	90.61	14.12 - 54.09

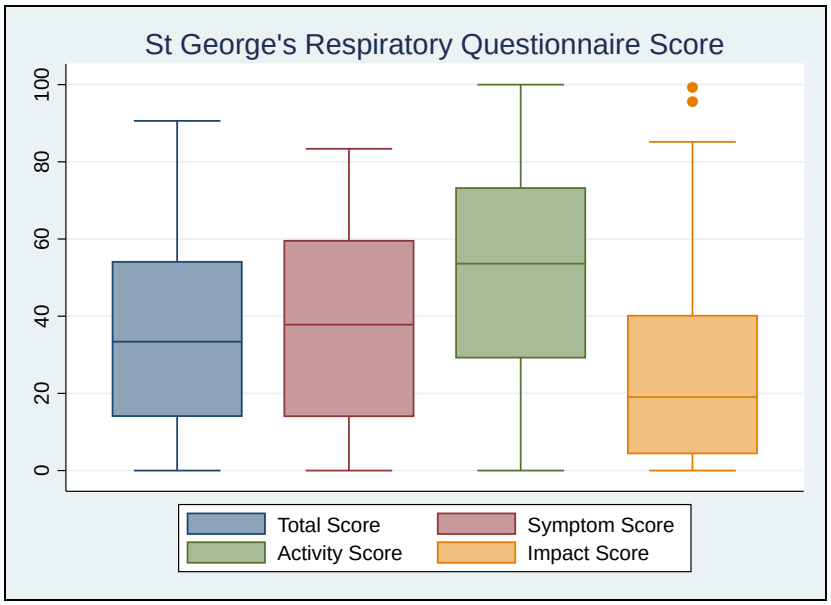

Figure 6: SGRQ scores at Visit 1 for all subjects.

5.5.8. Respiratory medication

Thirty-nine subjects (36.5%) reported use of at least one respiratory medication, the most common being short-acting beta-agonist use (SABA) in 29.9% of subjects [see Table 17]. Only 16.8% reported inhaled corticosteroid (ICS) use and 3.7% use of a LABA, while 35 (32.7%) reported use of respiratory medication for more than six months of the previous year.

Table 17: Use of respiratory medication in enrolled subjects.

(n=107)	**n**	**%**
Subjects not using respiratory medication	68	63.6%
Subjects using respiratory medication	39	36.5%
Number of concurrent medications:		
1	17	15.9%
2	11	10.3%
3	9	8.4%
4	2	1.9%
5	0	0.0%
Medication use		
SABA	32	29.9%
SAMA	10	9.4%
LABA	4	3.7%
(LAMA)	0	0.0%
ICS	18	16.8%
Theophylline	10	9.4%
Subjects using medication on most days	24	22.4%
In last year, number of months of medication use		
0 months	68	64.2%
0 - 3 months	1	0.9%
4 - 6 months	2	1.9%
7 - 9 months	1	0.9%
10 - 12 months	34	32.1%
unknown	1	0.9%

SABA – short-acting beta agonist
SAMA – short-acting antimuscarinic agent
LABA – long-acting beta agonist
LAMA – long-acting antimuscarinic agent
ICS – inhaled corticosteroid

5.6. Follow-up cohort: spirometry

A total of 106 of 107 subjects provided spirometry of acceptable quality at Visit 1. NHANES III reference equations and lower limit of normal (LLN) for Caucasians were applied.

5.6.1. FEV1:FVC

Of the 106 subjects, 94 (88.7%) demonstrated airflow obstruction (defined as FEV1:FVC <0.7) before administration of a bronchodilator (BD). This persisted after the bronchodilator in 90 subjects (84.9%). The mean post-BD FEV1:FVC was 0.58 (sd 0.140; range 0.27-0.90) [see Table 18 and Figure 7].

Table 18: Pre- and post-bronchodilator FEV1:FVC <0.70.

	Pre-BD No Obstruction	**Pre-BD Obstruction**	**Total**
Post-BD No Obstruction	8	8	**16**
Post-BD Obstruction	4	86	**90**
Total	**12**	**94**	**106**
			Obstruction defined as FEV1:FVC <0.7

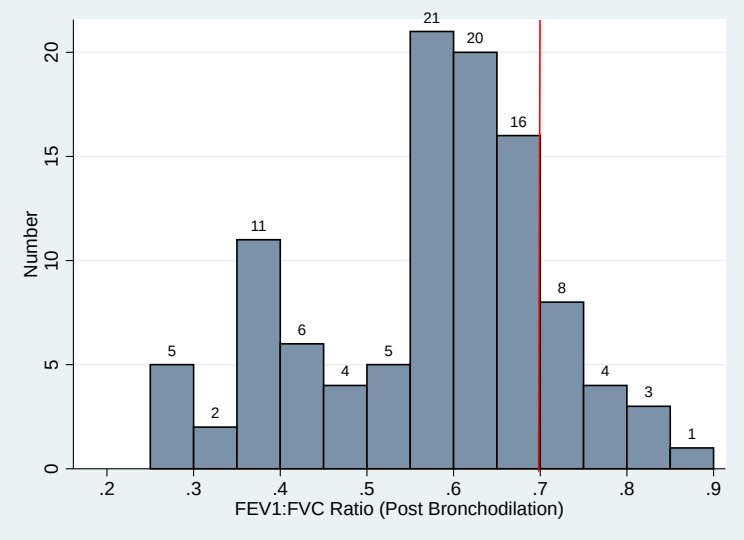

Figure 7: Distribution of post-bronchodilator FEV1:FVC.

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Using NHANES-III prediction equations, and a definition of airflow obstruction (AFO) as a post-BD FEV1:FVC less than the lower limit of normal (LLN) for age, 79 of 106 (74.5%) subjects had AFO and 27 (25.5%) hadn't. Thus, the LLN definition resulted in 11 subjects being reclassified as not having AFO [see Table 19]. Nine of these 11 (81.8%) subjects were older than 65 years of age, 7 (63.6%) were over 70 years, and 5 (45.5%) were over 75 years.

Table 19: Comparison of airflow obstruction (AFO) using the fixed ratio and lower limit of normal (LLN) definitions.

		LLN definition		
		AFO –ve	**AFO +ve**	**Total**
Fixed ratio definition	**AFO –ve**	16	0	16
	AFO +ve	11	79	90
	Total	27	79	106

5.6.2. FEV1 and FVC

The post bronchodilator values obtained at Visit 1 for FEV1 and FVC (in litres and percentage predicted) are presented in Table 20, Figure 8, Figure 9, Figure 10 and Figure 11. FEV1 and FVC reported in litres were not normally distributed. There was no significant difference in FVC (as percentage predicted) between those with AFO and those without, using either the lower limit of normal (t-test p=0.8135) or the fixed ratio definition for AFO (t-test p=0.3288).

Table 20: Post bronchodilator FEV1 and FVC of all subjects at Visit 1.

	n	Mean	Median	sd	Min	Max	IQR
Post BD FEV1							
FEV1 (in litres)	106	1.63	1.51	0.662	0.61	3.57	1.12 - 2.13
FEV1 (% pred)	106	62.73	64.8	18.94	23.1	101.9	46.2 - 77.2
AFO by LLN	*79*	*57.08*	*55.8*	*17.63*	*23.1*	*101.9*	*41.2 - 70.9*
AFO by fixed ratio	*90*	*59.76*	*60.8*	*18.42*	*23.1*	*101.9*	*42.3 - 73.1*
No AFO (by fixed ratio)	*16*	*79.45*	*79.3*	*12.10*	*61.5*	*99.9*	*69.2 - 88.7*
Post BD FVC							
FVC (in litres)	106	2.86	2.66	0.983	1.21	5.7	2.09 - 3.45
FVC (% pred)	106	82.64	82.64	15.36	48.17	128.86	71.82 - 94.21
AFO by LLN	*79*	*82.85*	*83.18*	*16.01*	*48.17*	*128.86*	*71.34 - 94.49*
AFO by fixed ratio	*90*	*83.26*	*83.52*	*15.58*	*48.17*	*128.86*	*71.88 - 94.49*
No AFO (by fixed ratio)	*16*	*79.17*	*79.10*	*14.00*	*54.56*	*104.55*	*69.15 - 87.83*

BD = bronchodilator
AFO = Airflow obstruction
LLN = lower limit of normal

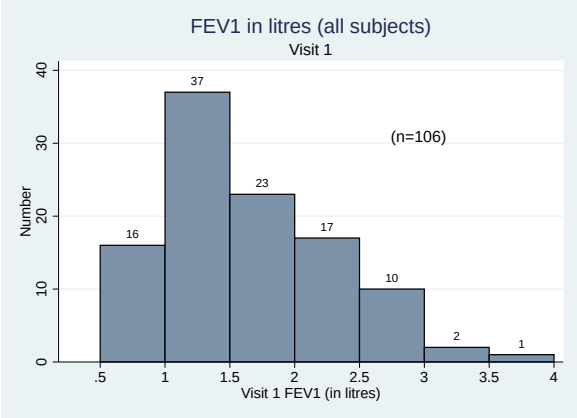


Figure 8: Visit 1 post-bronchodilator FEV1 for all subjects (litres).

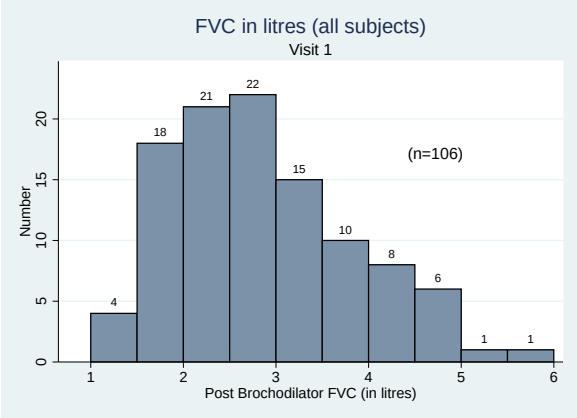


Figure 10: Visit 1 post-bronchodilator FVC for all subjects (litres).

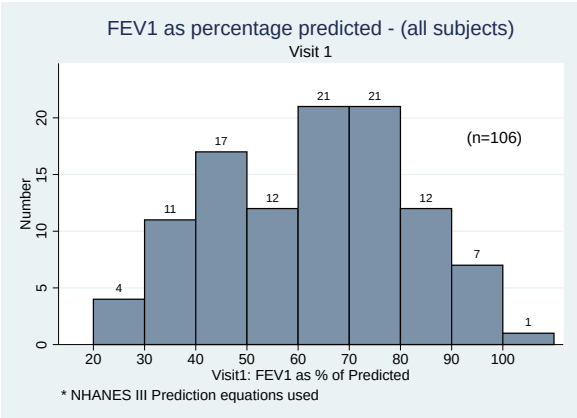


Figure 9: Visit 1 post-bronchodilator FEV1 for all subjects (% predicted).

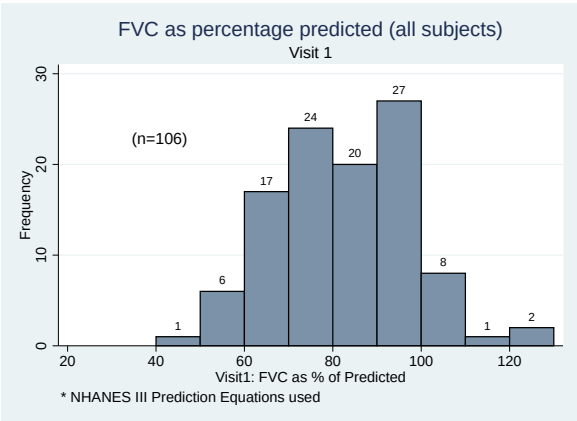


Figure 11: Visit 1 post-bronchodilator FVC for all subjects (% predicted).

5.6.3. FEV1 reversibility

Reversibility, which is defined as an increase in FEV1 following bronchodilator administration of more than 200 mL and more than 12.0%, was found in 32.1% subjects, in 34.4% with AFO (31 of 90 subjects) and 18.8% without AFO (3 of 16 subjects) [see Table 21, Figure 12 and Figure 13].

Table 21: Reversibility of FEV1 in subjects with and without post-bronchodilator airflow obstruction.

	No Obstruction	%	Obstruction	%	Total	%
No Reversibility	13	81.3%	59	65.6%	72	67.9%
Reversibility	3	18.8%	31	34.4%	34	32.1%
Total	16	100.0%	90	100.0%	106	100.0%

Reversibility = >200 mL and 12% increase in FEV1
Obstruction = FEV1:FVC <0.7

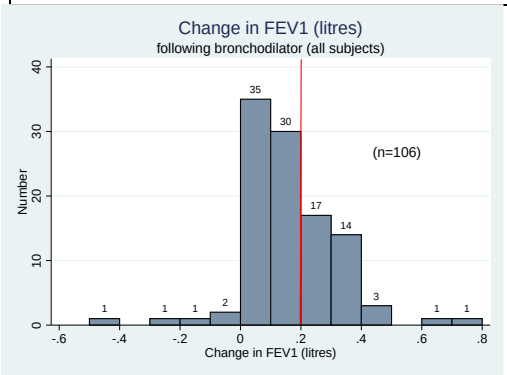


Figure 12: Change in FEV1 (litres) postbronchodilator (all subjects).

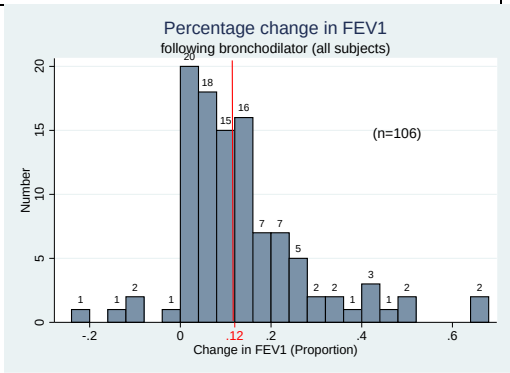


Figure 13: Percentage change in FEV1 post bronchodilator (all subjects).

5.6.4. Comparison of GOLD staging in BOLD 2005 and Follow-up study

The GOLD staging (in 2005) included (n=106) and not included in the Follow-up study (n=90) is presented in Table 22 and Table 23, together with a comparison of staging in 2005 and 2010 for subjects included in both studies (n=106).

During BOLD 2005, of the 106 subjects included in the lung function analysis at Visit 1, 17 were GOLD stage 1 (16.0%), 65 were GOLD stage 2 (61.3%), 23 were GOLD stage 3 (21.7%) and 1 was GOLD stage 4 (0.9). Twenty-one subjects (19.8%) deteriorated by a GOLD stage, 27 subjects (25.5%) improved, and 58 subjects (54.7%) remained in the same GOLD stage. Change in staging was as follows:

- Deterioration in GOLD staging was seen in:
    - 29.4% (5 of 17) of those previously in GOLD stage 1
    - 20.0% (13 of 65) of GOLD stage 2
    - 13.0% (3 of 23) of GOLD stage 3.

- Improvement in GOLD staging was seen in:
    - 35.3% (6 of 17) of those previously in GOLD stage 1
    - 23.1% (15 of 65) of GOLD stage 2
    - 21.7% (5 of 23) of GOLD stage 3
    - and 100.0% (1 of 1) of GOLD stage 4.
- No Change in GOLD staging between the studies was observed in:
    - 35.3% (6 of 17) of those in GOLD stage 1
    - 56.9% (37 of 65) of GOLD stage 2
    - 65.2% (15 of 23) of GOLD stage 3
    - none of GOLD stage 4.

In addition, 16 subjects no longer had AFO in 2010 (i.e. FEV1:FVC was $\geq$0.70). Six of these (37.0%) had previously been in GOLD stage 1 in 2005, nine (56.3%) in GOLD stage 2, and one (3.7%) in GOLD stage 3 in 2005.

Of the 90 subjects who remained obstructed at the GOLD stage:

- 21 subjects deteriorated (23.3%)
- 11 subjects improved (12.2%)
- 58 subjects remained the same (64.4%).

Table 22: GOLD stage in 2005 for subjects not included in the Follow-up study.

	Died	Moved	Excluded	Declined	Unable to perform spirometry	Total
GOLD stage (in 2005)						
1	6	3	2	5		**16**
2	20	5	7	11	1	**44**
3	15	3	5	3		**26**
4	4	0	0	0		**4**
Total	45	11	14	19	1	**90**

Table 23: Comparison of GOLD stage in 2005 (BOLD study) with 2010 (Follow-up study) for included subjects.

	GOLD stage at Follow-up study (2010)					
GOLD stage at BOLD Study (2005)	Not Obstructed	**1**	**2**	**3**	**4**	**Total**
1	**6**	6 *(54.6%)*	5 *(45.5%)*	0 *(0.0%)*	0 *(0.0%)*	**11**
2	**9**	6 *(10.7%)*	37 *(66.1%)*	12 *(21.4%)*	1 *(1.8%)*	**56**
3	**1**	1 *(4.6%)*	3 *(13.6%)*	15 *(68.2%)*	3 *(13.6%)*	**22**
4	**0**	0 *(0.0%)*	0 *(0.0%)*	1 *(100%)*	0	**1**
Total	**16**	13	45	28	4	**90**
Highlighted cells demonstrate no interval change in GOLD stage		*Percentage = % of 2005 GOLD stage (for subjects with obstruction only, n=90)*				

5.6.5. Longitudinal change in lung function

5.6.5.1. Change in FEV1 between BOLD and Follow-up study

The post-bronchodilator FEV1 values (in litres) and changes between studies were not parametrically distributed. Results are presented in Table 24, Figure 14 and Figure 15. There was a significant decline in FEV1 (litres) between the BOLD and Follow-up studies (Wilcoxon $p<0.0001$), with a median decline of 0.155L.

Table 24: Comparison of FEV1 (litres) between BOLD and Follow-up studies (all subjects).

	n	Mean	Median	sd	Min	Max	(IQR)	
BOLD FEV1	106	1.78	1.64	0.655	0.65	4.01	(1.28 - 2.27)	*Wilcoxon*
Follow-up FEV1	106	1.63	1.51	0.662	0.61	3.57	(1.12 - 2.13)	*p<0.0001*
Change in FEV1	106	-0.149	-0.155	0.324	-1.37	1.8	(-0.30 - 0.00)	

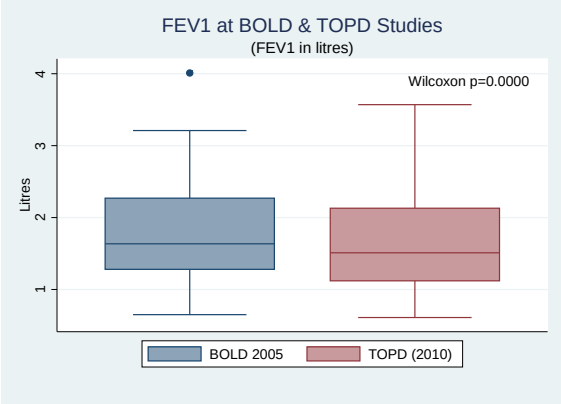


Figure 14: Comparison of FEV1 (litres) between BOLD and Follow-up studies (all subjects).

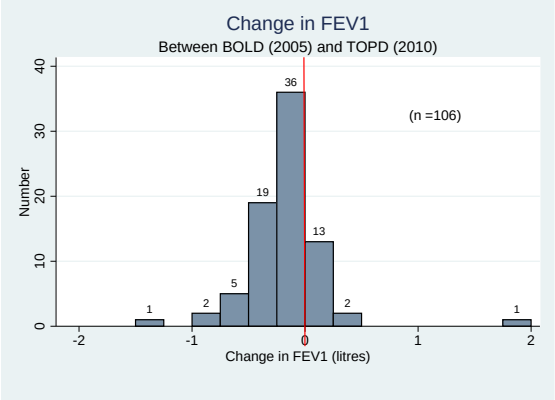


Figure 15: Change in FEV1 (litres) between BOLD and Follow-up studies (all subjects).

Comparison of the changes in FEV1 (as percentage predicted) using the Student's t-test for parametrically distributed variables [Table 25, Figure 16 and Figure 17], showed no difference in the FEV1 (% predicted) between the studies (t-test for paired samples: p=0.316).

Table 25: Comparison of FEV1 (% predicted) between BOLD and Follow-up studies.

	n	Mean	Sd	Min	Max	
BOLD FEV1	106	0.638	0.169	0.278	1.058	*t-test for paired samples; p=0.316*
Follow-up FEV1	106	0.627	0.189	0.231	1.019	
Change in FEV1 (% predicted)	106	-0.011	0.110	-0.334	0.476	

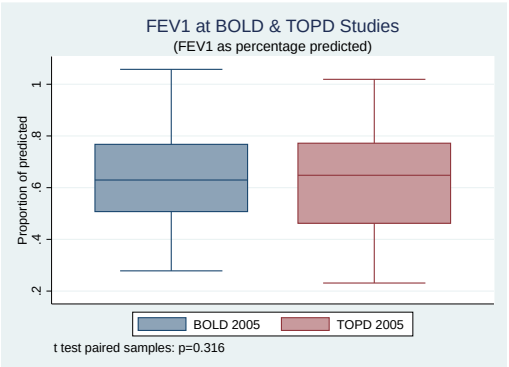


Figure 16: Comparison of FEV1 (% predicted) between BOLD and Follow-up studies.

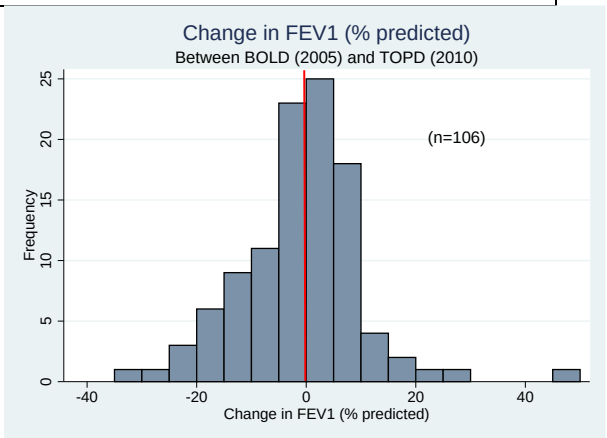


Figure 17: Change in FEV1 (% predicted) between BOLD and Follow-up studies.

The decline in FEV1 (L) was assessed according to GOLD stage at the BOLD 2005 study – a non-parametric variable. Although the mean decline in FEV1 appeared to be larger in the higher GOLD staging groups, when the appropriate non-parametric tests (i.e. Kruskal-Wallis test) were used to compare median values, no significant difference was found (Kruskal-Wallis; p=0.479). As GOLD stage 4 only comprised of one subject at follow-up, this stage was omitted from the analysis [see Table 26, Figure 18 and Figure 19].

Table 26: Change in FEV1 (mL) between the studies, grouped according to GOLD stage at BOLD study (2005).

	n	Mean	Median	sd	Min	Max	IQR
GOLD 1	17	-202	-210	191	-440	140	-378: -60
GOLD 2	65	-177	-120	282	-1 370	470	-300: -40
GOLD 3	23	55	-170	464	-700	1 800	-250: 50
GOLD 4	1	370	370	-	-	-	-
Overall	**106**	**-149**	**-155**	**324**	**-1 370**	**1 800**	**-300: -000**

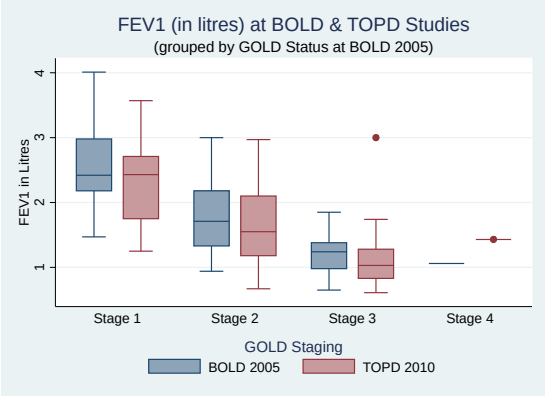


Figure 18: FEV1 (litres) at BOLD and Follow-up studies, grouped according to GOLD stage in 2005.

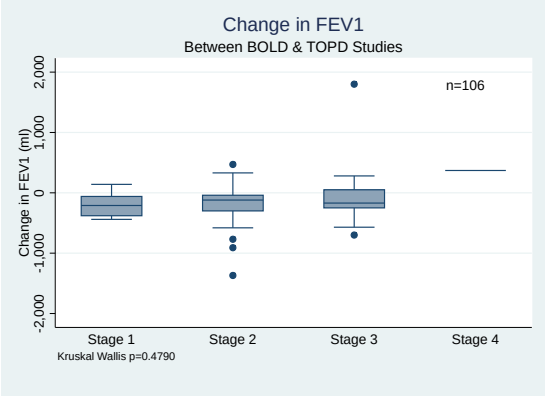


Figure 19: Change in FEV1 (mL) between studies, grouped according to GOLD stage in 2005.

The median rate of change in FEV1 (mL per year), a non-parametrically distributed variable, was 28.93 mL/yr [see Table 27 and Figure 20]. No significance difference in rate of decline was found between subjects in the different GOLD stages assessed at the BOLD 2005 study (Kruskal-Wallis; p=0.247).

Table 27: Rate of change in FEV1 (mL per year) between BOLD and Follow-up studies.

(n=106)	**Mean**	**Median**	**sd**	**IQR**	**Min**	**Max**
Rate of FEV1 Change (mL/yr)	-28.29	-28.93	59.71	(-54.76 – 0.00)	-246.26	317.15

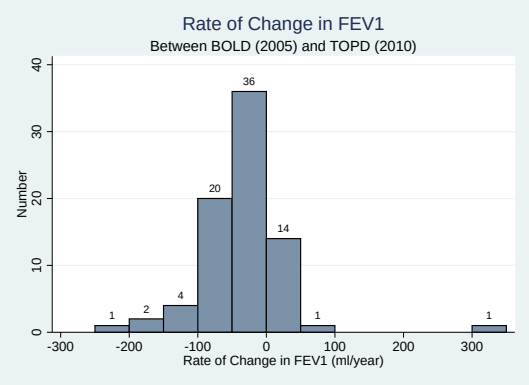


Figure 20: Rate of change in FEV1 (mL/ yr) between BOLD and Follow-up studies.

To examine the potential effect of treatment of airflow limitation on the results of spirometry in the Follow-up study, the association between rate of change in FEV1 and use of respiratory medication was assessed. No association between the use of any respiratory medication, LABA or ICS use alone; and rate of change of FEV1 was found (Wilcoxon p=0.168, p=0.868 and p=0.614, respectively). However, subjects who used SABAs showed a greater rate of decline in FEV1 (Wilcoxon p=0.0467) [see Table 28]. However, this is likely to be reverse causation, with SABAs being dispensed for subjects with worsening lung function.

Table 28: Rate of change of FEV1 according to use of short-acting beta$_2$-agonist (SABA).

	n	**Mean**	**Median**	**IQR**	**Min**	**Max**
No SABA use	74	-21.33	-21.21	-49.41: 5.65	-246.26	317.15
SABA use	32	-44.39	-35.05	-71.10: -12.54	-172.57	68.08

5.6.5.2. Change in FVC between the BOLD and Follow-up study

Between the BOLD and Follow-up studies, there was a significant decline in FVC (in litres) (Wilcoxon p=0.0419), but not FVC (% predicted) (Wilcoxon p=0.773) [see Table 29, Figure 21 and Figure 22].

Table 29: Comparison of FVC between BOLD and Follow-up studies.

(n=106)	**Mean**	**Median**	**sd**	**Min**	**Max**	**IQR**	
FVC (litres)							
At BOLD 2005	2.97	2.77	0.943	1.2	5.75	2.22: 3.54	*Wilcoxon*
At TOPD 2010	2.86	2.66	0.983	1.21	5.7	2.09: 3.45	*p=0.0419*
Change in FVC	-92.45	-75.00	564.04	1820	2730	-420.00: 200.00	
FVC (% Predicted)							
At BOLD 2005	82.54	82.29	17.29	42.86	147.40	69.08: 92.08	*Wilcoxon*
At TOPD 2010	82.64	82.64	15.36	48.17	128.86	71.82: 94.21	*p=0.773*
Change in FVC (%)	0.104	2.478	16.287	-61.263	52.352	-9.384: 10.423	

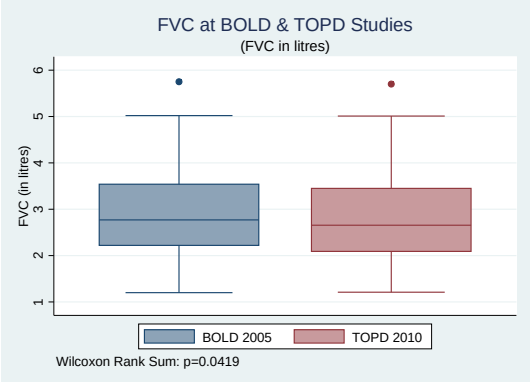


Figure 21: Comparison of FVC (in litres) between BOLD and Follow-up studies.

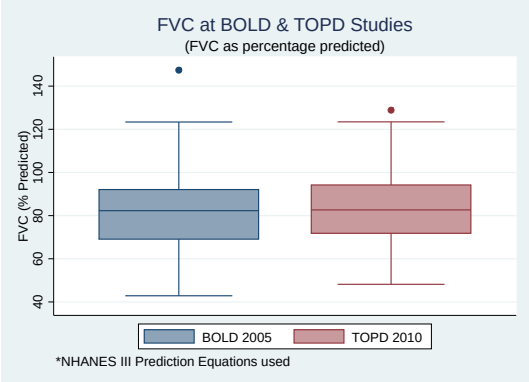


Figure 22: Comparison of FVC (% predicted) between BOLD and Follow-up studies.

A significant difference in the change in FVC, in both millilitres (Kruskal-Wallis p=0.0073) and % predicted (Kruskal-Wallis p=0.0101), was observed when analysing according to GOLD stage at the BOLD 2005 study [see Table 30, Figure 23 and Figure 24].

Subjects in GOLD stage 1 at BOLD 2005 had a significantly greater decline in FVC compared to subjects in both GOLD stages 2 and 3 (p=0.0171

and p=0.0025, respectively). However, there was no significant difference in the change in FVC between subjects in GOLD stages 2 and 3 (p=0.136). GOLD stage 4 comprised of only one subject, and was therefore excluded from the analysis.

Table 30: Change in FVC between studies, grouped according to GOLD stage at BOLD 2005 study.

	n	Mean	Median	sd	Min	Max	IQR		
Change in FVC (in mL)									
GOLD 1	17	-386	-350	406.9	-1160	500	-520:	-190	
GOLD 2	65	-99	-80	510.1	-1820	1540	390:	190	*Kruskal-Wallis*
GOLD 3	23	119	140	714.9	-1050	2730	-160:	270	*p=0.0073*
GOLD 4	1	510	510	-	-	-	-	-	
Total	**106**	**-92**	**-75**	**564**	**-1820**	**2730**	**-420:**	**200**	
Change in FVC (% predicted)									
GOLD 1	17	10.09	-8.49	17.159	-61.26	16.00	-16.98:	1.43	
GOLD 2	65	0.39	2.12	14.746	-33.45	52.35	-8.47:	10.42	
GOLD 3	23	6.16	8.02	17.02	-23.89	52.14	-3.31:	15.50	*Kruskal-Wallis*
GOLD 4	1	15.45	15.45	-	-	-	-	-	*p=0.0101*
Total	**106**	**0.10**	**2.48**	**16.29**	**-61.26**	**52.35**	**-9.38:**	**10.42**	

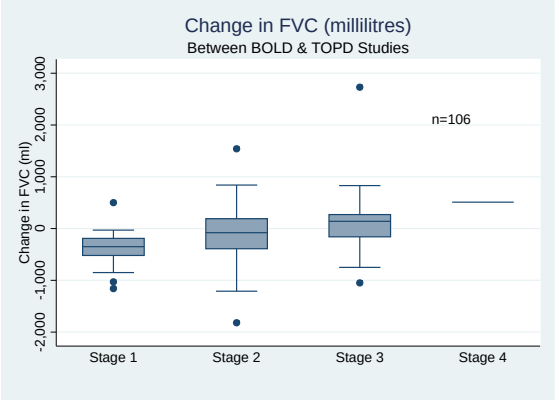


Figure 23: Change in FVC (mL) between studies, grouped according to GOLD stage in 2005.

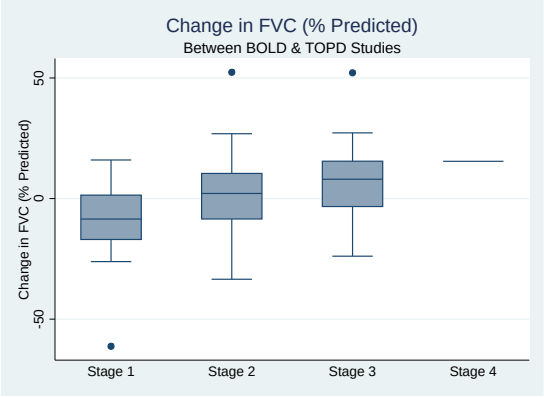


Figure 24: Change in FVC (% predicted) between studies, grouped according to GOLD stage in 2005.

5.6.5.3. Change in FEV1:FVC between BOLD and Follow-up study

The absolute FEV1:FVC, a non-parametric variable, was found to be significantly lower in the Follow-up study compared with the BOLD study (Wilcoxon p=0.0047). The mean change in FEV1:FVC, a parametric variable, decreased by 2.5% (mean) [see Table 31].

When comparing the change in FEV1:FVC between GOLD stage groups in BOLD 2005, only a trend to significance was observed, with GOLD stages 2 and 3 demonstrating a greater decline (ANOVA; p=0.091). GOLD stage 4 (n=1) was excluded from this analysis.

Table 31: Comparison of FEV1:FVC between BOLD & TOPD studies.

	n	Mean	sd	IQR		Min	Max	
BOLD 2005	106	60.0	9.00	(55.86 -	67.22)	35.44	70.21	*Wilcoxon*
TOPD 2010	106	57.5	13.96	(46.13 -	66.20)	27.01	89.60	*p=0.0047*
	n	**Mean**	**sd**	**Min**	**Max**			
Change in FEV1:FVC								
Overall	106	-2.50	9.76	-25.45	22.33			
By GOLD stage (2005)								
GOLD 1	17	1.98	8.871	-9.52	19.23			
GOLD 2	65	-3.08	9.659	-25.45	22.33			*ANOVA*
GOLD 3	23	-4.52	10.116	-21.17	19.18			*p=0.091*
GOLD 4	1	5.20	-	-	-			

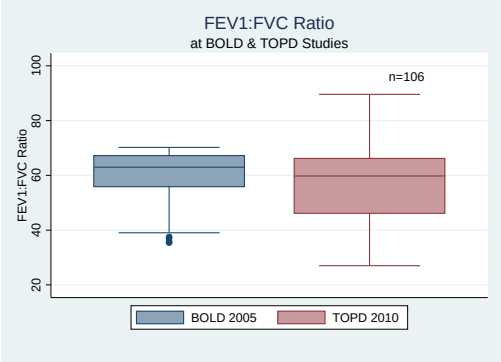


Figure 25: Comparison of FEV1:FVC between BOLD and TOPD studies.

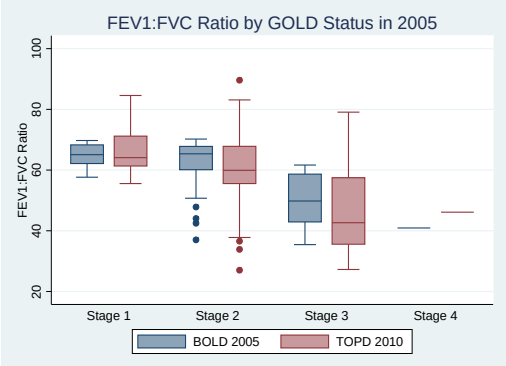


Figure 26: Comparison of FEV1:FVC between studies, grouped according to GOLD stage in 2005.

5.7. Change in symptoms between BOLD and Follow-up studies

The change in two reported symptoms between the two studies was assessed: dyspnoea, according to the MRC Dyspnoea Scale; and presence or absence of chronic cough. When comparing the MRC Dyspnoea scores [see Table 32]: 35 (32.7%) of 107 subjects reported the same dyspnoea score in both studies, while 58 (54.2%) reported worsening, and 14 (13.1%) had improved.

Table 32: Comparison of MRC Dyspnoea scores between the BOLD 2005 and Follow-up study.

		BOLD study (2005)					
		MRC 1	**MRC 2**	**MRC 3**	**MRC 4**	**MRC 5**	**Total**
Follow-up study (2010)	**MRC 1**	21	5	3	1	0	**30**
	MRC 2	10	2	1	0	0	**13**
	MRC 3	10	1	5	0	1	**17**
	MRC 4	5	6	8	4	3	**26**
	MRC 5	6	1	6	5	3	**21**
	Total	**52**	**15**	**23**	**10**	**7**	**107**

The presence of a chronic cough [see Table 33] was reported by 48 subjects (44.9%) in 2005 and 63 (58.9%) in 2010. Twenty-five subjects (23.4%) reported the development of a chronic cough, while 10 subjects (9.3%) previously reporting a chronic cough, reported no chronic cough in the Follow-up study.

Table 33: Comparison of presence of chronic cough between the BOLD 2005 and Follow-up study.

	BOLD study (2005)			
Follow-up study (2010)		**Cough**	**No cough**	**Total**
	Cough	38	25	63
	No cough	10	34	44
	Total	48	59	107

5.8. Summary of Findings

Mortality

The mortality among subjects identified with CAO was high. Almost a quarter of all subjects identified with CAO in the BOLD 2005 study had died by the five-year follow-up, 57.7% of whom had only mild or moderate airflow obstruction (i.e. GOLD stage 1 or 2 disease) in 2005. On multivariate analysis, only age and GOLD stage 4 disease was significantly associated with mortality. The commonest causes of death were cardiovascular (22.2%) and respiratory (17.8%) in nature; however, the cause of death was unknown in 46.7% of subjects.

Risk factors for CAO

The prevalence of a previous history of pulmonary TB was high. A total of 38.3% of subjects in the Follow-up study reported a previous episode of TB; in 52.6% this occurred before the age of 40 years.

Presence of CAO and decline in lung function and GOLD stage at Follow-up

At follow-up, only 84.9% of subjects had CAO defined by FEV1:FVC <0.70 and 74.5% when defined by LLN. The median decline in FEV1 between the studies was 155 mL (29 mL/yr), but this was not greater than the calculated age-related decline (i.e. when expressed as FEV1 % predicted). The decline in FEV1 did not appear to differ by GOLD stage of severity. By contrast, the decline in FVC (expressed in both litres and % predicted) was significantly greater in subjects with milder stages of disease.

In subjects with CAO, the GOLD stage had deteriorated between the studies in 23.3%, improved in 12.2% and was unchanged in 64.4%. However, this must be interpreted in the light of fact that a significant proportion of subjects had died.

Change in symptoms of COPD

A majority of subjects reported worsening of dyspnoea, and more subjects reported chronic cough at follow-up. However, some reported improvement and/or disappearance of a chronic cough.

Chapter 6. Results of the Assessment of the Diagnostic Accuracy of the BOLD Methods

The BOLD methodology involves use of questionnaires and a handheld spirometer suitable for use in participants' homes. This method, though highly suited for community-based surveys, of necessity involves compromise in terms of quality of spirometry and diagnostic precision. Specifically, compared with laboratory-based testing, it is not possible to standardise the time of day, washout of bronchodilators, and, possibly, of the quality of the spirometer used. However, in developing the BOLD methodology, the co-ordinators went to lengths to ensure that the spirometry results were of high quality, by careful assessment of the specifications and performance of the spirometer (the EasyOne ndd spirometer was selected); standardisation of test conditions, and the training and accreditation of those performing spirometry and providing centralised quality control and data entry [see page 46]. These measures make the data obtained suitable for making comparisons between different sites and countries. However, in common with most epidemiologic methods, the interests of field-use took precedence over diagnostic precision; to date, the impact of this has not been examined. This chapter provides detailed clinical evaluation by an experienced clinician, aided by comprehensive tests of lung physiology and imaging, of all participants considered to have COPD on the basis of the BOLD 2005 survey. Because the assessment was performed five years after the initial survey, in each subject, the clinical course served as an additional diagnostic feature. In this way, the diagnostic performance of the BOLD methods (both questionnaires and spirometry) was evaluated, in order to inform the interpretation of data obtained with this method.

6.1. Accuracy of diagnosis of Chronic Airflow Obstruction

A total of 106 subjects (54.1% of the original BOLD 2005 cohort of 196 subjects) were enrolled and underwent spirometry at Visit 1, and 103 (52.6%) at Visit 2 (there were three withdrawals before Visit 2). Using the fixed ratio definition of CAO (i.e. FEV1:FVC <0.70), 90 (84.9%) subjects had CAO, and 16 subjects (15.1%) did not. With the LLN definition, 79 subjects (74.5%) were defined as having CAO and 27 subjects (25.4%) were not. As expected, evidence of over-diagnosis of CAO in the elderly with the fixed-ratio methods was found; 9 of the 11 subjects (81.8%) with CAO by the fixed-ratio definition, but not the LLN-definition, were aged over 65 years. Seven of these were older than 70 years, and a further five were aged over 75 years.

6.2. Misdiagnosis: inclusion of subjects with asthma

Distinguishing between asthma and COPD on the basis of clinical features and spirometry is challenging, even for an experienced clinician, because the conditions lack pathognomonic clinical features and symptoms, and in many patients features of both may be present, the so-called Asthma COPD Overlap Syndrome (ACOS).[201] Thus, it is not surprising that the BOLD method does not attempt to exclude asthma in subjects with CAO, other than by excluding subjects under that age of 40 years when asthma is the more likely diagnosis.

To address the problem of distinguishing subjects with asthma from those with other causes of CAO, the approach adopted in the present study was to develop several categories of diagnosis, based on combinations of clinical features that are associated with increased likelihood of an asthma diagnosis. Thus, subjects were classified according to probability of an asthma diagnosis, ranging from highly likely (asthma) to probable (termed probable asthma). This approach also required consideration of features strongly associated with the diagnosis of COPD, that is, exposure history (smoking) and absence of reversibility after bronchodilator. In addition, as a

sensitivity assessment of these categories, all clinical data on each subject was reviewed by two pulmonologists and a 'clinician's diagnosis' on the presence or not of asthma was made on the balance of probabilities rather than strictly defined criteria. Additional points in the history of clinical presentation were also considered.

6.2.1. Definition of asthma

In the present study, the definition of asthma with a strong likelihood of asthma (here called asthma) required that participants fulfilled the following criteria: never a smoker (or light smoking history of less than five pack-years) AND a previous physician's diagnosis of asthma.

By this definition, a total of 11 out of 106 subjects (10.4%) had asthma. The results of spirometry, and association of an asthma diagnosis with CAO and reversibility are presented in **Table 34**:

- One subject with asthma had no airflow obstruction (FEV1:FVC >0.70) or reversibility. This participant was one of the 13 subjects in the whole study cohort with no CAO and no reversibility.
- Seven had airflow obstruction and no reversibility. These comprised seven of 59 (11.9%) subjects in the whole study cohort with this spirometry.
- Three had both airflow obstruction and reversibility; 10.7% (3 of 28) of subjects in the whole cohort with this pattern of spirometry.

Table 34: Association between asthma, chronic airflow obstruction and reversibility to bronchodilator.

	No CAO		**CAO**			
	No Revers	**Revers**	**No Revers**	**Revers**	**Total**	
No asthma	12	3	52	28	95	(89.6%)
Asthma	1	0	7	3	11	(10.4%)
Total	13	3	59	31	106	106

Revers = reversibility to bronchodilator
CAO = chronic airflow obstruction (i.e. FEV1:FVC<0.7)

6.2.2. Definition of probable asthma

A scoring method was used to define probable asthma: one point was allocated for each of the following:

- Never a smoker (or light smoking history of less than five pack-years)
- OR previous physician's diagnosis of asthma
- AND any two of the following three criteria:
    - positive skin prick test [defined on page 93]
    - history suggestive of allergic rhinitis
    - seasonal variations in symptoms.

A score of two or more was used to define the presence of probable asthma. Probable asthma was diagnosed in 19 of 106 subjects (17.9%). Of these subjects [see Table 35]:

- two had neither airflow obstruction (FEV1:FVC <0.70) nor reversibility; 2 of 13 subjects with this spirometry (15.4%).
- nine had airflow obstruction and no reversibility; 9 of 59 (15.3%) subjects in the whole study cohort with this spirometry.
- eight had both airflow obstruction and reversibility; 8 of 31 (25.8%) of subjects in the whole cohort with this pattern of spirometry.

Table 35: Association between probable asthma, chronic airflow obstruction and reversibility to bronchodilator.

	No CAO		CAO			
	No Revers	Revers	No Revers	Revers	Total	
No asthma	11	3	50	23	87	(82.1%)
Asthma	2	0	9	8	19	(17.9%)
Total	13	3	59	31	106	106

Revers = reversibility to bronchodilator
CAO = chronic airflow obstruction (i.e. FEV1:FVC<0.7)

6.2.3. Clinician's review of asthma diagnosis

Any subject, who exhibited reversibility to bronchodilator, did not have post-bronchodilator obstruction, or who had three or more suggestive features on

history, was submitted for manual review of asthma diagnosis by two pulmonologists. The suggestive features on history were: a non-smoker (or smoking history of less than five pack-years); a history suggestive of allergic rhinitis; seasonal variation in symptoms; a positive skin prick test; and a previous physician's diagnosis of asthma.

On this basis, a clinician's diagnosis of asthma was made in 18 of 106 subjects (17.0%). Of the 90 subjects with CAO, 15 (16.7%) were identified as asthmatic, while three of the remaining 16 subjects (18.8%) without CAO had asthma [see Table 36].

Table 36: Association between clinician's diagnosis of asthma, chronic airflow obstruction and reversibility to bronchodilator.

	No CAO		**CAO**		
	No Revers	**Revers**	**No Revers**	**Revers**	**Total**
No asthma	11	2	50	25	88
Asthma	2	1	9	6	18
Total	13	3	59	31	106

Revers = reversibility to bronchodilator
CAO = chronic airflow obstruction (i.e. FEV1:FVC<0.7)

6.3. Assessment of BOLD Instruments

6.3.1. Repeatability of questionnaires

In order to assess the repeatability of the BOLD questionnaire, two questions were selected where the responses were unlikely to have changed in the five years between studies. These were:

- How many years of formal education did you receive? ('years of schooling')
- What was the highest level of formal education that your father attained? ('years of fathers schooling')

A number of other questions were selected, for which a change from a positive response in BOLD 2005 to a negative response (in 2010) would

indicate an error of recall, either in the first or the second survey. These questions were:

- Have you ever smoked?
- Have you ever been told by a healthcare professional that you have had:
    - Heart attack?
    - Hypertension?
    - Diabetes?
    - Tuberculosis?

6.3.1.1. Concordance of answers to questions in 2005 and Follow-up

6.3.1.1.1 Years of schooling

One of 107 subjects had missing data for this question. In the remaining 106 subjects, 56 (52.8%) reported the same number of years of schooling in both studies [see Table 37], 24 (22.7% overall) reported a difference of two or more years, and five (4.7%) reported a difference of five years or more. The total reported number of years of schooling was similar between the studies (one sample median test, p=0.119). Using Bland-Altman analysis, a mean difference of –0.35 years in the reported number of years of schooling between the questionnaires is observed (sd = 2.06; 95% CI –4.48- +3.77) [see Figure 27 and Figure 28].

Table 37: Comparison of reporting number of years of schooling between BOLD and Follow-up studies.

Years of schooling	n	%
Same between studies	56	52.8%
Reported more years schooling in 2005 study	30	28.3%
Reported more years schooling in 2010 study	20	18.9%

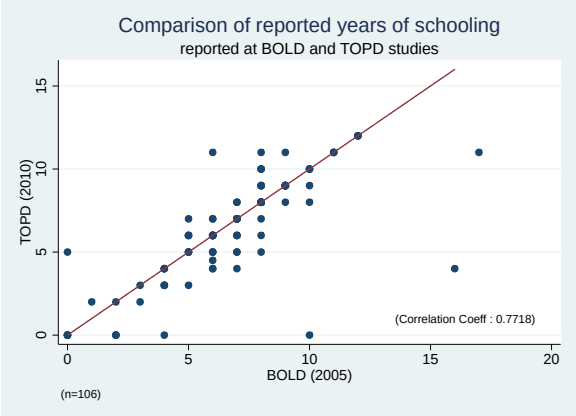


Figure 27: Scatter plot of the number of years of schooling reported in both studies.

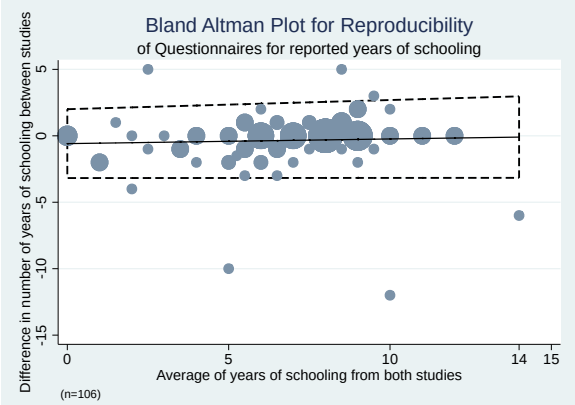


Figure 28: Bland- Altman plot of difference in reported number of years of schooling against the average number of years.

6.3.1.1.2. Fathers years of schooling

Possible responses to this question included: 'primary school', 'middle school', 'high school', 'college', 'technicon/university', 'none' or 'unknown'. Of the 107 subjects, 61 (57.0%) reported the same finding in both studies. Of the remaining 46 subjects (43.0%), 43 (93.5%) reported 'not knowing' at one of the two visits, but gave a definitive (discordant) response at the other. Of these 43 subjects, 33 reported 'not knowing' in the BOLD 2005 study, while only 10 reported 'not knowing' in the Follow-up study. This yields a kappa value of 0.238 [expected agreement 43.6%; actual agreement 57.0%; $p<0.0001$). The large number of discrepancies points to systematic error in this population. This may reflect a genuine lack of knowledge of the correct answer to this question, resulting in guesses that varied between visits.

6.3.1.1.3. Smoking status change

Of the 107 subjects analysed in 2005, 92 (86.0%) were classified on the basis of the questionnaire as smokers or ex-smokers. None of these reported being never smokers in 2010, confirming good repeatability of this question [see Table 38]. However, two additional subjects reported being smokers at the second study, possibly because they had begun to smoke. This was not interrogated further.

Table 38: Comparison of reporting of smoking status in 2005 and 2010.

		BOLD 2005 study		
Follow-up in 2010		Smoker	Never-smoker	Total
	Smoker	92	2	94
	Never-smoker	0	13	13
	Total	92	15	107

6.3.1.1.4. History of comorbidity

The comparison of subjects reporting comorbidities (heart disease, hypertension, diabetes or TB) in 2005 and 2010 is presented in Table 39. Two of the five subjects who reported heart disease in 2005 failed to report this in 2010, but an additional 13 reported this condition in 2010. Similarly, no subject who reported hypertension in 2005 changed their response in 2010, but an additional 23 reported hypertension in 2010. For diabetes, all but one continued to report diabetes in 2010, and an additional five subjects reported having this condition. Finally, only one of 34 subjects who reported a history of TB in 2005 gave a negative response to this question in 2010, but an additional seven subjects reported this disease in 2010.

An estimate of the repeatability of the above questions was performed using kappa values; however, incident pathology (i.e. developing disease between 2005 and 2010) had to be considered. When the incident disease was re-coded as 'no change', the resultant kappa values provided a conservative estimate of the repeatability of the questions. The kappa values (and 95% CIs) are presented below in Table 40.

Table 39: Comparison of reporting of disease between the BOLD 2005 and Follow-up study.

		BOLD study (2005)		
		Heart disease	**No heart disease**	**Total**
	Heart disease	3	13	16
	No heart disease	2	89	91
	Total	5	102	107
Follow-up study (2010)		**Hypertension**	**No hypertension**	**Total**
	Hypertension	30	23	53
	No hypertension	0	54	54
	Total	30	77	107

		Diabetes	**No Diabetes**	**Total**
	Diabetes	9	5	14
	No Diabetes	1	91	92
	Total	10	96	106
		Tuberculosis	**No tuberculosis**	**Total**
	Tuberculosis	34	7	41
	No tuberculosis	1	65	66
	Total	35	72	107

Table 40: Estimates of kappa values for question repeatability (excluding incident disease).

	kappa value	**95% CI**
For smoking status	1.00	(0.81 – 1.19)
For heart disease	0.74	(0.56 – 0.92)
For hypertension	1.00	(0.81 – 1.19)
For diabetes	0.94	(0.75-1.13)
For tuberculosis	0.98	(0.79 -1.17)
** incident pathology was recoded as "no change" (i.e. negative) in 2010*		

6.3.2. Assessment of spirometry

6.3.2.1. Reproducibility

The term reproducibility refers to a test performed on the same subjects, but under different conditions (e.g. different time, position of subject, observer etc.) When a test is performed on a subject under the same conditions, the term repeatability is used, and is not appropriate here.[202]

The reproducibility of the EasyOne ndd spirometer was considered by comparison of results obtained at Visit 1 and Visit 2 in two ways: first by direct comparison of the spirometric volumes and second by comparing the designation of subjects as having CAO or not, according to the FEV1:FVC.

A total of 56 subjects were included in this analysis. Of the 107 subjects at Visit 1, three had withdrawn by Visit 2, two were unable to perform spirometry, and one had missing data. Additionally, to limit the potential for confounding, subjects with more than 30 days between the

visits (n=4), and subjects that were required to withhold respiratory medication prior to Visit 2 (n=41), were omitted. Thus, the included subjects were stable on treatment that could affect airway caliber. The mean time between the visits was 10.8 days (median 10.5 days, sd=3.41 days, range 2-24 days).

For FEV1 measured with the EasyOne ndd spirometer, the correlation coefficient between values at Visits 1 and 2 was 0.9471 [see Figure 29]. However, using the Bland-Altman analysis, the mean difference was 0.0180 litres (sd=0.220, 95% CI –0.422- +0.458) [see Figure 30]. Thus, on a subsequent visit, the variation in FEV1 measurement ranged from 422 mL below or 458 mL above the initial measurement. Sixteen of 56 subjects (28.6%) had FEV1 values that differed by more than 150 mL between the visits.

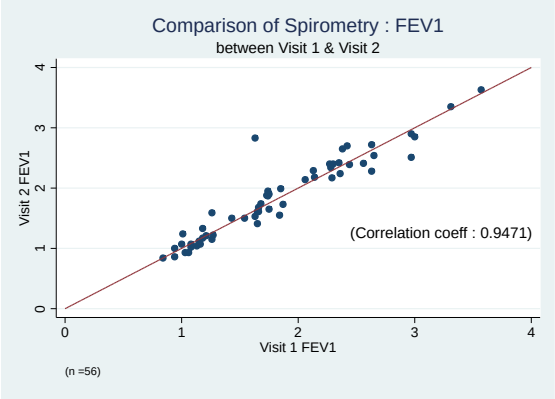


Figure 29: Comparison of FEV1 at Visit 1 & Visit 2 using EasyOne ndd spirometer.

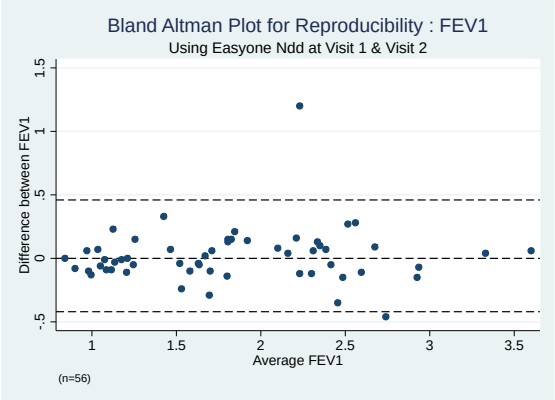


Figure 30: Bland-Altman plots for FEV1 reproducibility using EasyOne ndd spirometer.

The correlation coefficient for the FVC between Visits 1 and 2 was 0.9153 [see Figure 31], and in the Bland-Altman analysis, the mean difference was –0.003 litres (sd=0.448 litres, 95% CI –0.899- +0.894) [see Figure 32]. A total of 37 subjects (66.1%) had FVC measurements that differed by more than 150 mL between the visits.

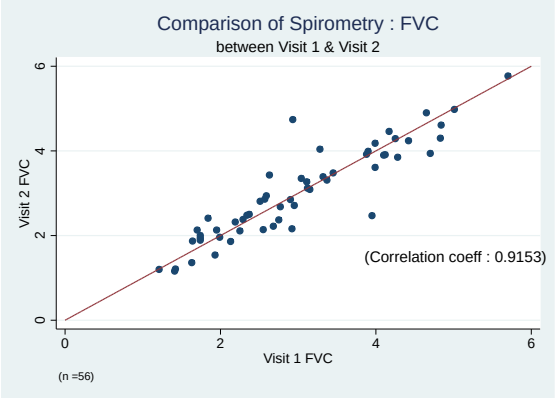


Figure 31: Comparison of FVC at Visit 1 and 2 using EasyOne ndd spirometer.

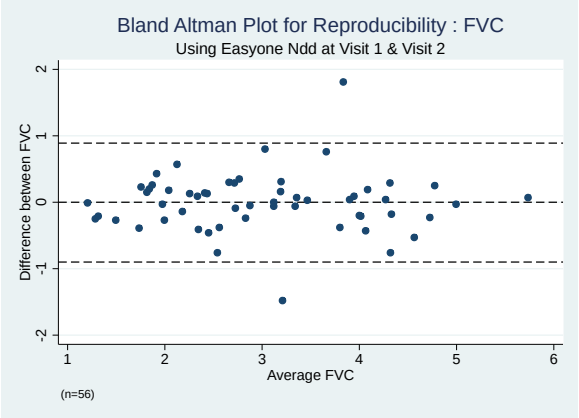


Figure 32: Bland-Altman plots for FVC reproducibility using EasyOne ndd spirometer.

The classification of subjects according to the presence or absence of CAO (defined as FEV1:FVC <0.70) at two visits (less than 30 days apart) using the same spirometers, was assessed. Discordance in classification of CAO status was found in 11 of 56 subjects (19.6%), but neither reading had a higher likelihood of diagnosing CAO [see Table 41]

Table 41: Correlation between assessments of CAO at Visit 1 and Visit 2 (less than 30 days apart) performed with the EasyOne nnd spirometer in subjects not receiving treatment for airways disease.

		Visit 1		
Visit 2		**No CAO**	**CAO**	**Total**
	No CAO	6	5	11
	CAO	6	39	45
	Total	12	44	56

6.3.2.2. Comparison of results of spirometry performed with the EasyOne ndd with Nspire office spirometers

Pre- and post-bronchodilator spirometry was performed at Visit 2 using two different spirometers: the handheld EasyOne ndd and the Nspire office spirometer [see page 68].

Of the possible 107 eligible subjects, three withdrew before Visit 2, one was unable to perform acceptable spirometry, and one had missing data. In the remaining 102 subjects, the correlation coefficient for FEV1

between the spirometers was 0.979 [see Figure 33], and on Bland-Altman analysis the mean difference was 0.0415 litres (sd 0.146, 95% CI –0.251-+0.333). Thus, difference in FEV1 measured by the handheld EasyOne ndd spirometer ranged from 250 mL lower to 333 mL higher than that measured by the Nspire spirometer [see Figure 34]. Twenty-three subjects (22.5%) had FEV1 values that differed by more than 150 mL between spirometers at the same visit [see Figure 35].

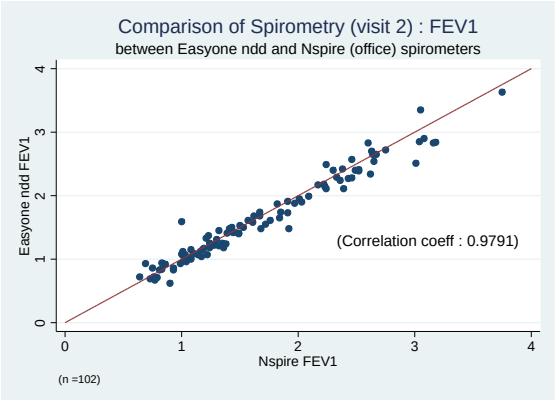


Figure 33: Comparison of FEV1 at Visit 2 using two different spirometers.

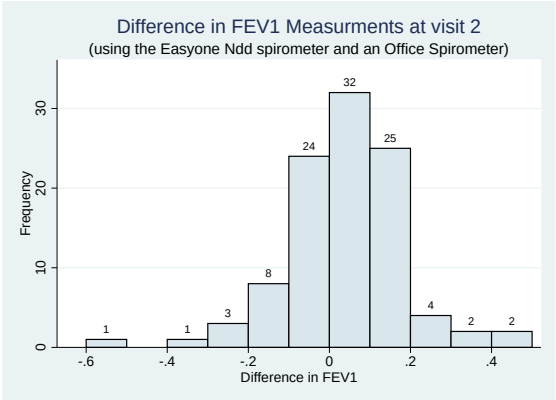


Figure 35: Difference in measurement of FEV1 at Visit 2 using two different spirometers.

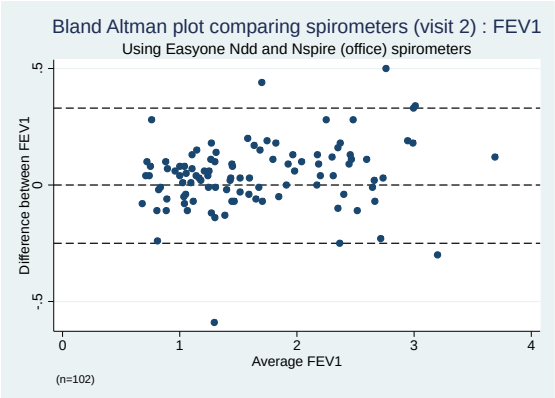


Figure 34: Bland-Altman plot comparing FEV1 using two different spirometers at Visit 2.

The assessment for the presence of CAO by the two spirometers at Visit 2 differed in 17 subjects (16.7%) [see Table 42], but neither spirometer was associated with a greater tendency to diagnose CAO.

Table 42: Classification in the assessment of CAO made with two spirometers at Visit 2.

		EasyOne Spirometer		
Nspire Spirometer		**No CAO**	**CAO**	**Total**
	No CAO	7	10	17
	CAO	7	78	85
	Total	14	88	102

6.4. Summary of findings

In the assessment of the methodology used during the Cape Town BOLD 2005 study, approximately 15.0% of subjects no longer had evidence of airflow obstruction. This discrepancy was higher (25.0%) when the LLN definition was applied. Apart from the well-described over-diagnosis in the elderly, the reasons for the high numbers of non-obstructed individuals is not clear, but could include: misdiagnosis and inclusion of asthmatic subjects; systematic measurement error in either the first or second study (e.g. variability in spirometry measurement or inadequate FVC manoeuvre at second visit); or the effect of treatment in some subjects. However, this last explanation is unlikely as no association between the use of respiratory medication and change in FEV1 was observed [see page 102].

Estimates of the prevalence of asthma in the Follow-up cohort ranged from 6.3%-18.8% in subjects without airflow obstruction, and from 11.1%-18.9% for those with airflow obstruction: 10.4% and 17.9% overall. Of these, a number with both CAO and a smoking history, are likely to be considered as asthma-COPD overlap syndrome (ACOS). However lack of definitive diagnostic criteria for this condition makes formal conclusions difficult, and even if the diagnosis is adopted, treatment approaches different to those for COPD and more similar to asthma, should be employed.[98]

Large variation in the reproducibility of FEV1, and especially FVC, between visits less than 30 days apart, were observed with the same handheld EasyOne ndd spirometers. This difference resulted in a change in the diagnosis of CAO in up to 19.6% of subjects.

Additionally, there was a large variation in FEV1 measurement between those obtained with the EasyOne ndd and the Nspire office spirometer used on the same occasion. In up to 16.7% of subjects this difference resulted in discordant assessment of CAO status.

However, these differences between the spirometer results appeared to be random (i.e. neither systematic nor unidirectional). Despite the discordant results, the total numbers of subjects with and without CAO remained similar. These results suggest that the EasyOne ndd provides a reasonably reliable estimate of the prevalence of CAO for epidemiological population-level research, but for clinical diagnosis and management results of spirometry need to be viewed with caution and, if necessary, repeated, as results from a single-test may be misleading. The use of additional tests with more accurate office equipment, and other lung function tests will further improve the accuracy of diagnosis in individual patients.

Chapter 7. Classification of Subjects according to Previous Pulmonary Tuberculosis Status

7.1. Introduction

The central hypothesis examined in the present study is whether chronic airflow limitation in patients with a history of previous pulmonary tuberculosis (PPTB) differs in terms of pathophysiology, natural history and responsiveness to treatment to that in patients without this risk factor for COPD. It is therefore crucial to correctly assign subjects as having had pulmonary tuberculosis or not. There is, however, no agreed or standardised method of retrospectively assessing PPTB status. This chapter compares different methods of investigating PPTB status and the approach adopted in the present study.

7.2. Measurement of PPTB status by questionnaire

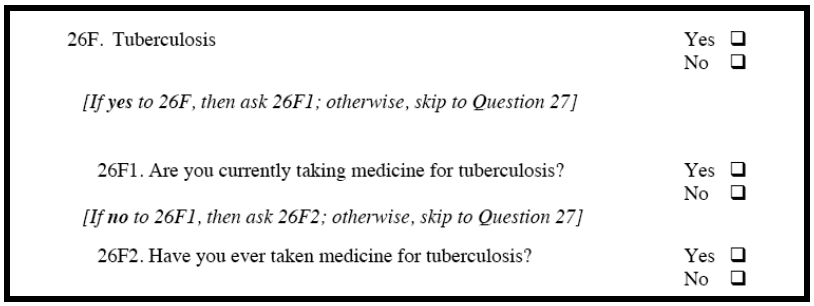
To assess the potential of using a more detailed questionnaire with which to assign subjects correctly, two questionnaires, the second being more comprehensive, were administered and compared.

7.2.1. BOLD Questionnaire

The BOLD Questionnaire, which was used in both the BOLD 2005 and Follow-up Study in 2010, contained the following questions [see **Figure 36**]:

- Has a doctor or other health care worker ever told you that you have had tuberculosis? (Question 26F)
    - (If yes) Are you currently taking medicine for tuberculosis? (Question 26F1)

- (If no) Have you ever taken medicine for tuberculosis? (Question 26F2)


26F. Tuberculosis Yes ❑ No ❑

[If yes to 26F, then ask 26F1; otherwise, skip to Question 27]

26F1. Are you currently taking medicine for tuberculosis? Yes ❑ No ❑

*[If **no** to 26F1, then ask 26F2; otherwise, skip to Question 27]*

26F2. Have you ever taken medicine for tuberculosis? Yes ❑ No ❑

Figure 36: BOLD Questionnaire questions ascertaining previous tuberculosis status.

Results from the BOLD questionnaire have been presented on page 88 and Table 8. In brief, of the 107 subjects included in the study at Visit 1, 41 subjects (38.3%) provided a positive response to question 26F (above) and reported a previous history of TB, whereas 66 subjects (61.7%) did not. One subject provided no data on past treatment received for PTB, but all of the remaining 40 subjects reported having received medication for tuberculosis previously, and none were currently on treatment.

7.2.2. Additional Tuberculosis Questionnaire

At follow-up in 2010, an Additional Tuberculosis Questionnaire (ATbQ) was developed and administered, and the results were compared with the BOLD questionnaire [see Appendix 2 – Additional Tuberculosis Questionnaire]. The ATbQ contained the following questions:

1. Were you ever diagnosed with tuberculosis?
2. (If yes) How many times were you treated for tuberculosis?

For every episode of tuberculosis, the subject was asked, if possible, to provide the following information:

- Date of diagnosis
- Site of infection

- Certainty or assurance that the diagnosis was communicated by the diagnosing healthcare worker
- Method of diagnosis
- Hospitalisation for treatment
- Duration of hospitalisation (if appropriate)
- Site of treatment (i.e. clinic)
- Duration of treatment
- Completion of treatment
- Resolution of symptoms
- Assessment as 'cured' by healthcare worker
- Failure to complete treatment.

Based on responses to this questionnaire, a specialist pulmonologist provided an opinion as to whether a diagnosis of PPTB could be made with certainty. The results of this questionnaire have been presented on page 89 and Table 9, Table 10,Table 11 and Table 12. In short, with the ATbQ, 39 subjects (36.4%) reported having had at least one episode of PPTB, while 68 subjects (63.6%) did not.

7.2.3. Comparison of questionnaires

Agreement of the PPTB status between the two questionnaires was 98.1% (expected agreement 53.2%), kappa value of 0.96 (95% CI 0.91-1.00).

In the two subjects lacking agreement between questionnaires:

- One subject reported having being treated for tuberculosis for three months as an outpatient before the diagnosis was changed to asthma.
- For the other subject, there was no obvious reason for the discrepant responses and it was considered by the study team to be an error of data entry in the BOLD questionnaire.

The concordance between the two questionnaires is reassuring. Potentially the wording of the BOLD questions is likely to record trials of PTB treatment (empiric short-term use of TB treatment), as a 'positive history of PTB' – even when treatment is stopped following evidence of a wrong diagnosis of TB. This did not appear to be a significant problem in the present study.

7.3. Assessment of PPTB status using chest X-ray

7.3.1. Description of method

Two experienced pulmonologists reported the chest X-rays of the 104 subjects (taken at Visit 2) of whom these were available. The readers were blinded to the subject information, including history of previous TB, and were asked to respond to the following questions:

- Is the chest X-ray completely normal? (Y/N)
- Is the chest X-ray consistent with previous tuberculosis? (Y/N)
- Is there hyperinflation on chest X-ray? (Y/N)
- Is there volume loss on chest X-ray? (Y/N) (Volume loss of both single lobes and of the whole lung was considered to be volume loss.)

In view of the wide variety of radiological changes that may be found after an episode of TB, such as: fibro-cavitatory changes; apical fibrosis and bands; cavitation; granulomas (which may or may not be calcified); bronchiectasis; lymph node calcification; and pleural fibrosis, the term 'consistent with previous tuberculosis' could not not defined. Instead, the two readers were asked to use their experience and clinical judgment to answer the questions.

Lack of agreement between the two readers after their first read was resolved during a consensus read, which was held on a different occasion, at which readers were blinded to their original responses, and a consensus decision was reached.

7.3.2. Findings

Of the 104 subjects with chest X-rays, both readers judged 47 subjects (45.2%) to have had PPTB, while 57 subjects (54.8%) were considered to have no evidence of PPTB. However, these were not always the same subjects. In 14 subjects, there was lack of concordance (i.e. lack of agreement into which category a subject fell). Thus, the overall kappa value

was 0.72 (95% CI 0.60-0.86), with an agreement between the readers of 86.5% (expected agreement = 50.5%).

At the consensus read, Reader 1 changed six results, and Reader 2 changed eight results, giving a consensus categorisation of 45 subjects (43.3%) as having chest X-ray evidence of PPTB, and 59 subjects (56.7%) without such evidence [see Table 43 and Figure 37].

Table 43: Results of the assessment of chest X-rays for features compatible with PPTB by two independent readers.

	Reader 1	%	Reader 2	%	Consensus	%
Previous TB	47	45.2%	47	45.2%	45	43.3%
No Previous TB	57	54.8%	57	54.8%	59	56.7%
Total	**104**	**100.0%**	**104**	**100.0%**	**104**	**100.0%**

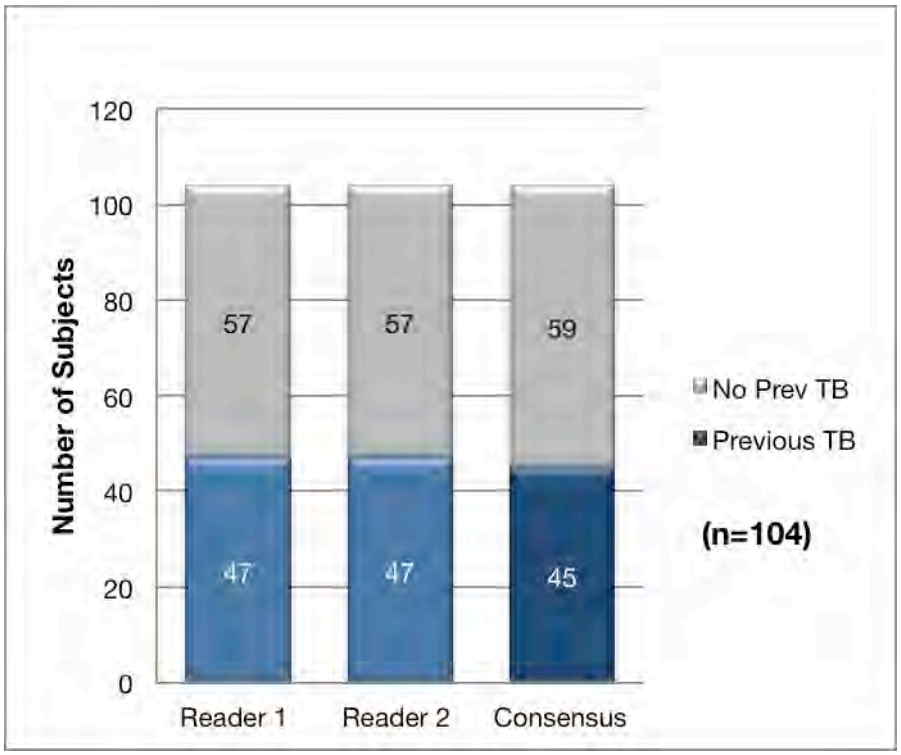


Figure 37: Results of the assessment of chest X-rays for features compatible with PPTB by two independent readers.

7.4. Measurement of PPTB status using CT scans

7.4.1. Description of method

Two consultant radiologists (one from UCLA and one from UCT) were blinded to all subject information and asked to review all 104 CT scans for evidence of PPTB. They were asked to comment on the following:

- Presence of the following changes, and likelihood that they were due to previous TB:
    - Apical changes
    - Nodules
    - Calcification
    - Lymph nodes
    - Pleural abnormalities
    - Other (not specified)
- Whether the CT scan showed evidence of PPTB (yes/no)
- A rating of their confidence that the radiological abnormalities reported were due to PPTB.

For estimation of likelihood, a Likert scale of 0 to 5 was used, with: 0, no evidence; 1, highly unlikely; 3, equivocal; and 5, highly likely due to PTB. Where there was disagreement between Reader 1 and 2 on PPTB status, a third reader (a pulmonologist) was asked to review and report on the scan. This arbitrating reader was blinded to both subject information and previous radiological assessments. Blinding was ensured by randomly including among the images, 26 CT scans on which the first two readers had agreed.

7.4.2. Findings

Reader 1 identified 62 subjects (59.6%) with and 42 subjects (40.4%) without CT changes consistent with PPTB. Reader 2 reported changes consistent with PPTB in 84 subjects (80.8%) and no changes in 20 subjects (19.2%) (kappa value: 0.43, 95% CI 0.27-0.60). There was 75.0% agreement between the readers (expected agreement 55.9%), representing discordance on 26 scans. The arbitrating reader differed with and changed 17 results from

Reader 2, and 9 results from Reader 1. Thus, the final categorisation of CT scans was: 71 subjects (68.3%) exhibited changes consistent with PPTB, and 33 (31.7%) did not [see Table 44 and Figure 38].

Table 44: Assessment of PPTB status, using CT scans, by two readers.

	CT Reader 1	%	CT Reader 2	%	CT Consensus	%
Previous TB	62	59.6%	84	80.8%	71	68.3%
No Previous TB	42	40.4%	20	19.2%	33	31.7%
Total	**104**	**100.0%**	**104**	**100.0%**	**104**	**100.0%**

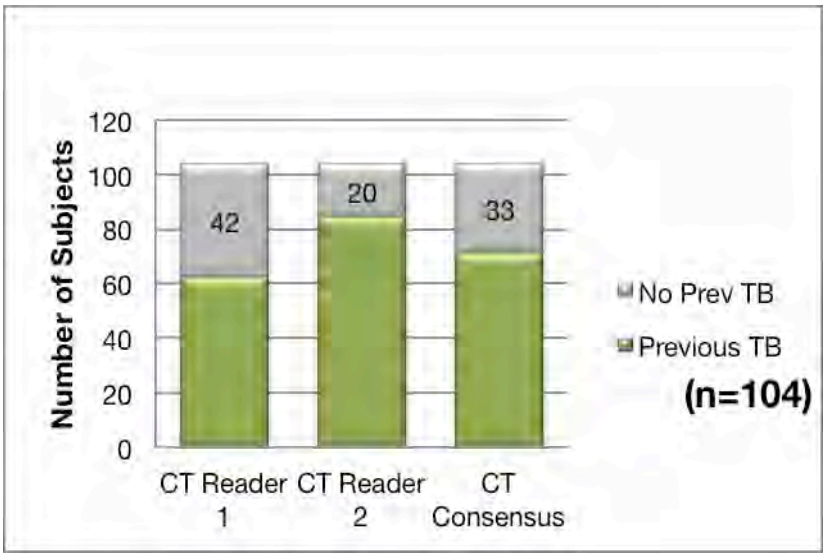


Figure 38: Assessment of PPTB status, using CT scans, by two readers.

The level of confidence of Readers 1 and 2 in their assignment of PPTB are presented in Table 45 and Figure 39.

Table 45: Reader confidence that changes observed on CT scan were due to PPTB.

	Reader 1	%	Reader 2	%
No Evidence	37	35.6%	5	35.6%
Highly Unlikely	4	3.9%	8	3.9%
Unlikely	2	1.9%	1	1.9%
Equivocal	8	7.7%	6	7.7%
Likely	7	6.7%	3	6.7%
Highly Likely	46	44.2%	81	44.2%
Total	**104**	**100.0%**	**104**	**100.0%**

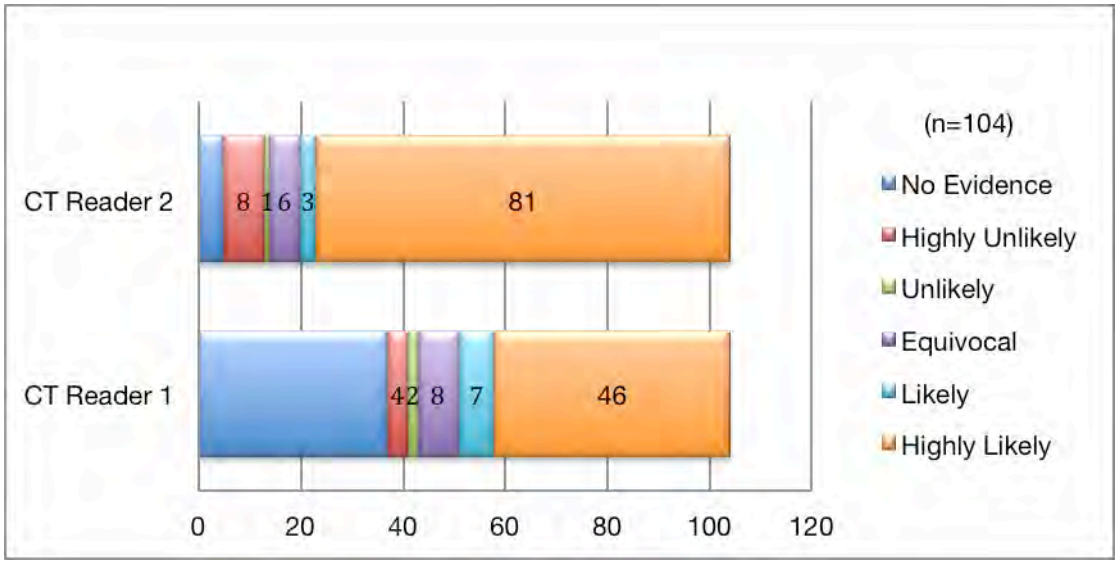


Figure 39: Reader confidence that changes observed on CT scan were due to PPTB.

7.5. Comparison of different methods of assigning PPTB status

Agreement between the different methods of assigning PPTB status was compared as follows:

7.5.1. Comparison of Additional TB Questionnaire and chest X-ray read

Of the 104 subjects with chest X-rays, there was concordance between the questionnaire and chest X-ray results in assigning TB status in 84 (80.8%), and discordance in 20 subjects (19.2%) with questionnaire, yielding a kappa value of 0.60 (95% CI 0.45-0.76; expected agreement 51.7) [see Table 46].

Table 46: Comparison of Additional TB Questionnaire (ATbQ) and chest X-ray read for assessing PPTB status.

		Chest X-ray		
		No Previous TB	**Previous TB**	**Total**
ATbQ	**No Previous TB**	52	13	65
	Previous TB	7	32	39
	Total	**59**	**45**	**104**

7.5.2. Comparison of Additional TB Questionnaire and CT scan read

There was poor agreement between questionnaire and CT scan in assigning PPTB status, with concordance in 68 (65.4%), and discordance in 36 of 104 subjects (34.6%), yielding a kappa value of 0.37 (95% CI 0.23-0.51; expected agreement 45.43%) [see Table 47].

Table 47: Comparison of Additional TB Questionnaire (ATbQ) and CT scan read for assessing PPTB status.

		CT Scan		
		No Previous TB	**Previous TB**	**Total**
ATbQ	**No Previous TB**	31	34	65
	Previous TB	2	37	39
	Total	**33**	**71**	**104**

7.5.2.1. Inter-reader concordance of CT scan assessment in subjects with a history of PPTB on questionnaire

Thirty-nine subjects gave a history of PPTB on ATbQ. In four of these subjects (10.3%), CT scan assessment of their PPTB status was discordant on the initial read by the two readers, the remainder (n=35) was concordant (i.e. assessed as evidence of PPTB). Two of the four discordant scans were ultimately adjudged to be consistent with PPTB, and two were adjudged to be inconsistent with PPTB.

7.5.2.2. Inter-reader concordance of CT scan assessment in subjects with no history of PPTB but CT scan evidence of PPTB

There were 34 subjects assessed as having PPTB on CT scan but not reporting a history of PPTB. Twenty-five of these CT scans (73.5%) were assessed by both readers as having evidence of PPTB (i.e. concordance), with the remaining nine CT scans (26.5%) yielding discordant assessment. The confidence with which PPTB was assessed by each of the readers for these 34 subjects is shown below in Table 48 and Figure 40.

Overall, the readers were confident or very confident (assigning high likelihood of PPTB) for the majority of CT images viewed.

Table 48: Reader confidence that observed CT scan changes were due to PPTB, in subjects with no history, but CT scan evidence for PPTB.

		Reader 1	%	Reader 2	%
Confidence of PPTB	**None**	6	17.65%	0	0%
	Very low	2	5.88%	0	0%
	Low	1	2.94%	0	0%
	Moderate	3	8.82%	1	2.94%
	High	5	14.71%	2	5.88%
	Very high	17	50.0%	31	91.18%
	Total	**34**	**100.0%**	**34**	**100.0%**

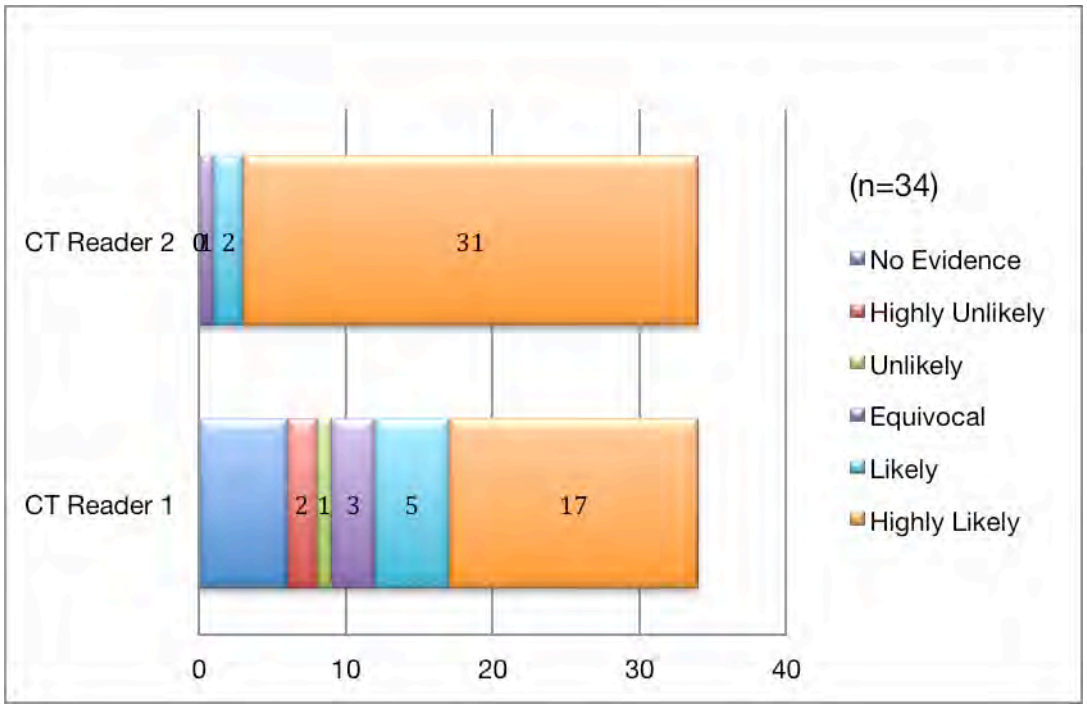


Figure 40: Reader confidence that observed CT scan changes were due to PPTB, in subjects with no history, but CT scan evidence for PPTB.

7.5.3. Comparison of chest X-Ray and CT scan reads

Assignment of PPTB status by chest X-ray and CT scans was concordant in 70 (67.3%) and discordant in 34 of 104 subjects (32.7%), yielding a kappa value of 0.38 (95% CI 0.23-0.53, expected agreement 47.5%) [see Table 49]. This lack of agreement was chiefly due to the greater sensitivity of CT scans.

Table 49: Comparison of chest X-ray and CT scan reads for assessing of PPTB status.

		CT scan		
		No Previous TB	**Previous TB**	**Total**
Chest X-ray	**No Previous TB**	29	30	59
	Previous TB	4	41	45
	Total	**33**	**71**	**104**

7.6. Analysis of grouping

The overlap of results of the three methods (ATbQ, chest X-ray and CT scan) for assessing PPTB status is presented in Table 50 and Figure 41.

Table 50: Grouping of subjects after assessment of PPTB status by Additional TB Questionnaire (ATbQ), chest X-ray and CT scan reads.

n=104		**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Group 5**	**Group 6**	**Group 7**	**Group 8**
Evidence for PPTB	**ATbQ**	+ve	+ve	+ve	-ve	+ve	-ve	-ve	-ve
	Chest X-ray	+ve	+ve	-ve	+ve	-ve	+ve	-ve	-ve
	CT Scan	+ve	-ve	+ve	+ve	-ve	-ve	+ve	-ve
	Number	31	1	6	10	1	3	24	28
	%	29.8%	1.0%	5.8%	29.8%	1.0%	2.9%	23.1%	26.9%

The majority of subjects showed agreement between the three methods of establishing PPTB status (i.e. 31 of 104 subjects were positive for PPTB by all three methods, and in 28, all three tests were negative). CT scan adjudged 24 subjects as PPTB alone, while a further six were assessed as PPTB by both CT scan and questionnaire, but not by chest X-ray. An additional 10 were assessed as PPTB by CT scan and chest X-ray, but not by questionnaire. Five subjects were adjudged as having PPTB by either questionnaire or chest X-ray, but not by CT scan. Their details are as follows:

- Two subjects were considered false negatives for PPTB assessed by CT scan, as both gave convincing histories for fully treated PPTB, and one had chest X-ray assessment supporting PPTB.

- Three subjects were adjudged as being true negatives for PPTB, as chest X-rays were thought to show evidence for PPTB, but both history and CT scans were negative.

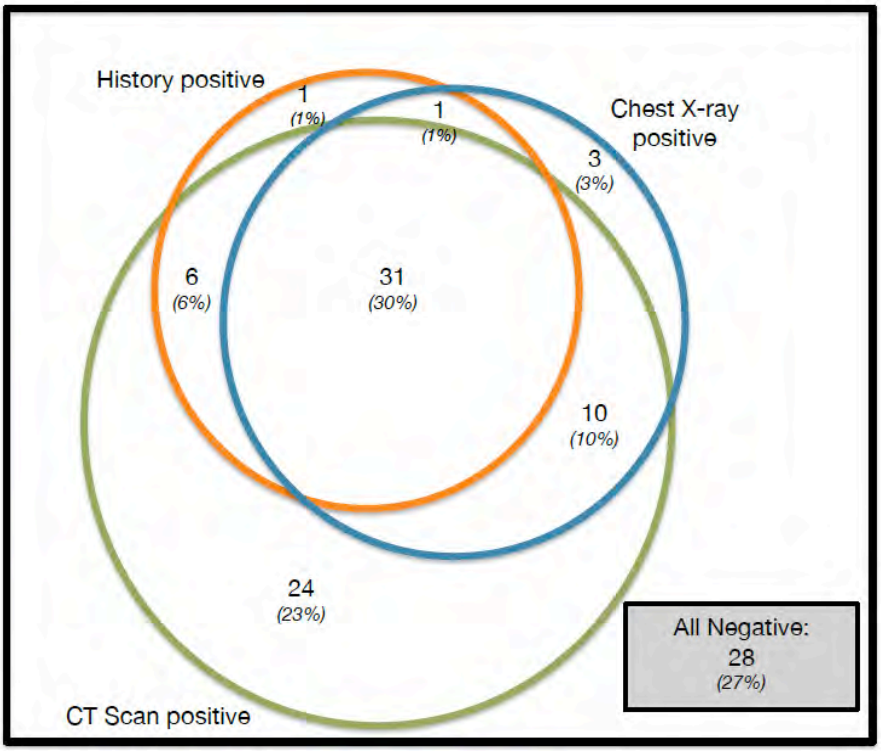


Figure 41: Assignment of PPTB status by questionnaire (ATbQ), chest X-ray and CT scan (n=104).

Thus, CT scanning misclassified two subjects as false negatives, and chest X-ray misclassified three subjects as false positives.

7.7. Composite definition of PPTB status for use in the TOPD

To assess the role of PPTB in CAO, it was important that only subjects with a very low likelihood of PPTB be included in a no PPTB group. A high negative predictive value ('rule out test') was therefore required to minimise potential for type II statistical error. For this reason, the categorisation employed in this study was a composite of both the Additional TB Questionnaires and CT scan assessments. Categories of subjects were defined as follows:

- Definite Previous Tuberculosis (DPTB) (n=39, 37.5%)

Subjects with a positive history in the Additional TB Questionnaire as having PPTB.

- Probable Previous Tuberculosis (PrPTB) (n=34, 32.7%)
  Subjects without a history of PPTB, but having CT scan evidence of PPTB.
- No Previous Tuberculosis (NPTB) (n=31, 29.8%)
  Subjects with neither a history of PPTB according to the ATbQ, nor evidence of PPTB on CT scan.

In some analyses, subjects in the DPTB and PrPTB groups were combined in the category Previous Pulmonary Tuberculosis (PPTB) (n=73).

7.7.1. Performance of questionnaire alone for ruling out PPTB

In this analysis, the performance of questionnaire alone using the ATbQ was compared to the above composite definition of PPTB. The ATbQ categorised 39 of 104 subjects as having PPTB, with the remaining 65 as not. Thus, compared to the above definition, the ATbQ incorrectly categorised 34 subjects (32.7%) as not having PPTB (i.e. false negatives), yielding a sensitivity of 53.4% (95% CI 42.1-64.4%); and negative predictive value (NPV) of 47.7% (95% CI 36.0-59.6%) (by definition, specificity and PPV were 100.0%) [see Table 52].

7.7.2. Performance of chest X-ray alone for ruling out PPTB

Similarly, the performance of chest X-ray alone was compared with the history and CT scan-based composite definition above, and yielded a sensitivity of 57.5% (95% CI 46.1-68.2%) and specificity of 90.3% (95% CI 75.1-96.7%), with three (2.9%) false positives and 31 (29.8%) false negatives [see Table 52].

7.7.3. Performance of alternative definition of PPTB status using questionnaire and chest X-ray

An alternative classification for PPTB using questionnaire and chest X-ray (but not CT scan) was compared with the questionnaire/CT scan-based composite definition described above.

This alterative classification categorised subjects as follows:

- Definite Previous Tuberculosis (n=39, 37.5%)
  Subjects with a history of PPTB regardless of chest X-ray findings.
- Probable Previous Tuberculosis (n=13, 12.5%)
  Subjects without a history of previous PTB but radiological evidence of PPTB on chest X-ray.
- No Previous Tuberculosis (n=52, 50.0%)

Subjects with neither a history nor chest X-ray evidence of PPTB.
Comparisons of the preferred composite and above alternative definitions of PPTB are shown in Table 51.

Table 51: Comparison of CT-based composite definition of PPTB status with the alternative classification using chest X-ray and questionnaire.

		Chest X-ray-based definition			
		NPTB	**PrPTB**	**DPTB**	**Total**
CT-based composite definition	**NPTB**	28	3	0	31
	PrPTB	24	10	0	34
	DPTB	0	0	39	39
	Total	52	13	39	104

The alternative history/chest X-ray-based classification mischaracterised 24 subjects (23.1%) as NPTB, when they had PrPTB by the preferred classification (i.e. false negatives), while three subjects (2.9%) were misclassified as PrPTB when they had NPTB (i.e. false positives). Thus, the overall misclassification rate was 26.0% (27 of 104 subjects).

Using the alternative questionnaire/chest X-ray classification and combining the Definite and Probable PPTB groups into a Previous TB (PPTB) group, the performance of this classification had a sensitivity of 67.1% (95% CI 55.7-76.8%), specificity of 90.3% (75.1%-96.6%), PPV of 94.2% (95% CI 84.4-98.0%) and NPV of 53.9% (95% CI 40.5-66.7%) [see Table 52]. Therefore, this method performs well as a rule-in test, but not as a rule out when the presence of previous PTB needs to be determined with a high-degree of certainty.

Table 52: Comparison of the composite definition of PPTB with questionnaire alone, chest X-ray alone, or combined questionnaire and chest X-ray (alternative definition).

	Composite Definition of PPTB*						
	PPTB	**NPTB**	**Total**	**Sn**	**Sp**	**PPV**	**NPV**
Questionnaire							
PPTB	39	0	39				
NPTB	34	31	65				
Total	**73**	**31**	**104**	53.4%	- #	100.0%	47.7%
Chest X-ray							
PPTB	42	3	45				
NPTB	31	28	59				
Total	**73**	**31**	**104**	57.5%	90.3%	93.3%	47.5%
Alternative definition using questionnaire and chest X-ray							
PPTB	49	3	52				
NPTB	24	28	52				
Total	**73**	**31**	**104**	67.1%	90.3%	94.2%	53.9%

**Composite Definition used both questionnaire and CT scan (as defined in text)*
 # Specificity not calculated as formed part of Composite Definition (therefore would be 100%)

7.8. Conclusion

Determining whether a patient has had, or has a strong likelihood of having had, pulmonary tuberculosis (PTB) is important in several clinical and research settings. Both epidemiological and immunological research require the correct classification of PPTB status to isolate the effects attributable to TB, while in clinical practice and drug research it remains important to establish PPTB status prior to commencing therapy that may impair the immune host-response to mycobacterial infection, for example, when using biological agents. There is, however, no gold-standard test for PPTB and commonly used methods have limitations.

The undisputed method for confirming PPTB is historical evidence (preferably in contemporaneous clinical reports) that infection with *Mycobacterium tuberculosis (Mtb)* has been confirmed bacteriologically. However, this information is seldom available, particularly in cross-sectional epidemiologic studies. Thus, although highly specific, this method lacks sensitivity and has a low negative predictive value. Reasons for the low yield

include: limited access to or incomplete clinical records, population mobility, and the limitations of sputum examination (smear-negative cases).

Self-reporting, the usual method in cross-sectional surveys[14,17,18] is subject to recall and reporting bias. A markedly lower prevalence of PPTB using history, as compared to chest X-ray findings, is common, as recently reported in the large BIOBANK cohort study.[26] In theory, both the questions used and the method of administration (i.e. self vs. investigator-administered) may influence the results. For example, the question 'have you ever been diagnosed with TB?' differs from 'have you ever been given TB treatment?'. The latter assumes a correct and bacteriological diagnosis, which may not be the case, particularly in high-burden settings where a trial of treatment is commonly used. In spite of these potential sources of imprecision, in the present study the kappa value for the comparison of the BOLD and more comprehensive ATbQ was 0.96, differing by only two subjects.

Other methods for assessing previous infection with Mtb (although not specifically PPTB) are the tuberculin skin test (TST) and Interferon Gamma Release Assays (IGRA). Although useful in developed countries, with a low-burden of TB, for diagnosing latent TB infection (with a high negative-predictive value), these tests are positive in the majority of adults in high-burden settings, regardless of TB status, and are therefore unhelpful as a rule-out test.[203] For this reason, neither TST nor IGRAs were used in the present study.

Radiology, predominantly chest X-ray, has been used in a number of studies to assess whether subjects have had PPTB.[26,158] Although the radiological changes of active TB are well known,[152] identifying and correctly attributing abnormalities to a previous bout of PTB is more difficult and no validated criteria for this have been proposed. The usual clinical question is whether a lesion represents active rather than healed disease, with the question of whether the change is compatible with healed PTB as a secondary consideration. However, in settings where even healed PTB needs to be excluded, even subtle changes may be significant and, as demonstrated in the current study, a CT scan identifies such abnormalities in

almost twice as many patients as a chest X-ray. Recognised lesions suggesting healed PTB include: fibrotic scars, nodules (with discrete borders or calcified), upper lobe changes with volume loss, and blunting of the costophrenic angles.[155,204] Applying strict and limited diagnostic criteria may increase the specificity of the diagnosis, but reduces sensitivity.

When developing an approach to using composites of evidence of PPTB to provide an accurate method for ruling out PPTB it was necessary to compare the yields and concordance between the different tests, and combinations thereof. Various methods were considered.

Discrepant Analysis compares two tests (e.g. questionnaire and chest X-ray) and employs a third test as the 'resolver test' to distinguish, in this instance, true positives (PPTB) from true negatives. However, among other weaknesses of the method, the resolver test is required to be a gold standard test and preferably independent of both initial tests. Additionally, this method most likely leads to upward bias in the sensitivity and specificity of the initial test, as not all subjects are exposed to the resolver test.[205].

An alternate approach is Latent Class Analysis, which models imperfect tests, called manifest variables, to identify different subtypes of cases, which are defined by the unobservable outcome, called latent variables (i.e. the true diagnosis). Results from the imperfect tests can be used to estimate true diagnostic status, sensitivity, specificity and prevalence. In the current study, the conditions required were not met, including the lack of adequate numbers of test (here only two tests) and lack of independence of the tests.[205]

For the present study, a Composite Reference Standard was used, which combined different and imperfect tests using pre-specified rules to determine disease status (e.g. presence of PPTB).[205] As the objective was a rule-out test, the most sensitive test (CT scan-based) was combined with the most specific test (clinical history of PPTB). Partial validation of the results of CT scan was the fact that all but two subjects with a history of PPTB had CT features compatible with this.

Thus, the use of a CT-based classification system that includes clinical history was adopted for the present study and is proposed as the best option in high-prevalence TB areas as a rule-out test for PPTB. History alone resulted in a misclassification rate of up to 32.7%, with a sensitivity of only 53.4%, and when combined with chest X-ray had a sensitivity of 67.1% and specificity of 90.3%, but misclassified 26.0% of subjects. In the absence of a better gold standard, the use of a history plus CT-based classification system described above is advised as the reference standard if PPTB needs to be excluded with a degree of certainty.

In the light of the above findings, the following composite was used in the study of TOPD:

1. Definite Previous Tuberculosis (DPTB): Subjects with a history of PPTB, based on the Additional Tuberculosis Questionnaire, almost all of who had CT scan evidence of PPTB.
2. Probable Previous Tuberculosis (PrPTB): Subjects without a history of PPTB, but with changes on CT scan compatible with PPTB.
3. No Previous Tuberculosis (NPTB): Subjects with neither a history of PPTB, nor evidence of PPTB on a CT scan of the chest.

In some analyses, DPTB and PrPTB groups were combined as Previous Pulmonary Tuberculosis (PPTB), for two-way comparison with NPTB.

Chapter 8. Results of Clinical Endpoints: Symptoms and Lung Physiology

8.1. Introduction

This chapter presents an analysis of the lung physiology data and clinical endpoints, comparing and contrasting the results for subjects with and without evidence of previous pulmonary tuberculosis (PPTB).

The data for this analysis was obtained at Visits 2 and 3. Prior to Visit 2, subjects who were on respiratory medications were required to observe a 'washout' period [see page 68]. Between Visits 2 and 3, subjects were administered oral prednisone (20 mg daily) and formoterol (long-acting $beta_2$-agonist) (24 mcg pMDI twice daily), as discussed on page 70. The interval between Visit 2 and 3 was a minimum of two and a maximum of four weeks.

The results obtained with the Nspire (office) spirometry were used for this analysis. A comparison of results obtained with the EasyOne ndd (handheld spirometer) and Nspire spirometers at Visit 2 are presented in Chapter 6 (page 123). For the present study subjects were classified as having Previous Pulmonary TB (PPTB) – either Definite Previous TB (DPTB) or Probable Previous TB (PrPTB) – or No Previous TB (NPTB), as defined in the previous chapter.

8.2. Analysis of the full cohort

A total of 104 subjects participated in both Visits 2 and 3. One subject was unable to perform acceptable spirometry, but measurements of DL_{CO} and whole body plethysmography were acceptable. Of these subjects, 31 (29.8%) were classified as having NPTB, 39 (37.5%) as DPTB and 34 (32.7%) as PrPTB [see Figure 42].

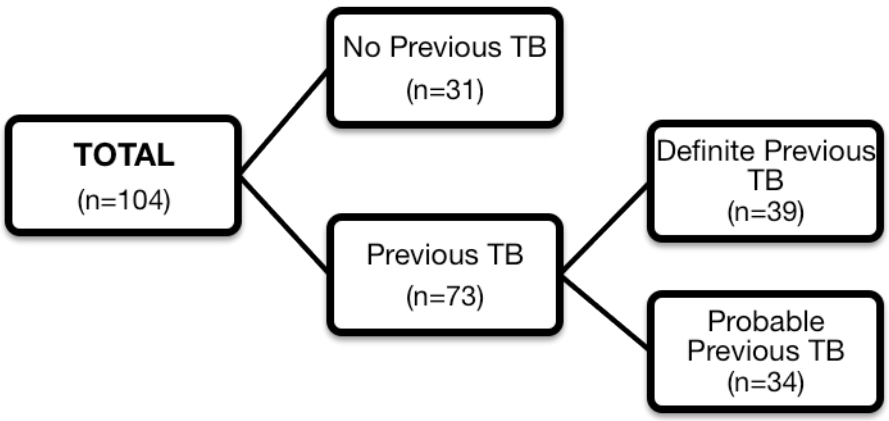


Figure 42: Classification of subjects according to PPTB status, used in the analysis of lung physiology.

8.2.1. Smoking status and chronic bronchitis

8.2.1.1. Smoking status

Smoking status, being both a major confounder and potential effect-modifier, was assessed using data collected in the Additional Smoking Questionnaire.

The smoking status of subjects according to the PPTB status is presented in Table 53. A significantly greater proportion of subjects with PPTB were smokers (either ex- or current smokers) compared to subjects without TB (93.2% vs. 77.4%, respectively, Chi2: p=0.022). The proportion of subjects who were smokers was 94.9% (37 of 39) of the DPTB group, 91.2% (31 of 34) of the PrPTB group, compared with 77.4% (24 of 31) of the NPTB group – a finding of borderline significance (Fisher's Exact: p=0.078, Chi2: p=0.063).

Of those with PPTB, 34.2% were ex-smokers (25 of 73) and 58.9% were current smokers (43 of 73). In those without PPTB, 41.9% were ex-smokers (13 of 31) and 35.5% were current smokers (11 of 31), which is a significant difference (Chi2: p=0.026). Of those with DPTB, 35.9% were ex-smokers (14 of 39) and 59.0% were current smokers (23 of 39). In the PrPTB group, 32.4% reported being ex-smokers (11 of 34) and 58.8% current smokers (20 of 34). On three-group analysis, the difference between groups was not statistically significant (Fisher's Exact Test p=0.125, Chi2: p=0.108).

Table 53: Comparison of smoking status according to PPTB status.

	NPTB	PPTB	*p-value*	*Test*	NPTB	DPTB	PrPTB	*p-value*	*Test*
Never smokers	**7**	**5**			**7**	**2**	**3**		
Ever smokers	**24**	**68**	***0.022***	***Chi2***	**24**	**37**	**31**	*0.078 (0.063*	*Fisher's Chi2)*
Ex-smokers	*13*	*25*			*13*	*14*	*11*		
Current	*11*	*43*	*[0.026*	*Chi2]*	*11*	*23*	*20*	*0.125 [0.108*	*Fisher's Chi2]*
Total	**31**	**73**			**31**	**39**	**34**		

In contrast to the above, comparison of the number of pack-years smoked (burden of smoking) was not significantly different between those with or without PPTB (Wilcoxon p=0.131), or on three-group analysis of those in the NPTB, DPTB and PrPTB groups (Kruskal-Wallis p=0.270) [see Table 54 and Table 55].

Table 54: Burden of smoking (pack-years) according to PPTB status: NPTB vs. PPTB.

Pack years	NPTB	sd	PPTB	sd	*p-value*	*test*
Mean	20.83	23.36	24.70	22.066	*n/a*	*n/a*
Median	13.05		21.20		*0.131*	*Wilcoxon*

Table 55: Burden of smoking (pack-years) according to PPTB status: three-group analysis.

Pack years	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
Mean	20.83	23.36	26.27	24.208	22.91	19.528	*n/a*	*n/a*
Median	13.05		22.00		19.86		*0.270*	*Kwallis*

8.2.1.2. Chronic bronchitis

In subjects with previous TB, chronic bronchitis (British MRC definition) was reported in 34.2% of subjects (25 of 73) with PPTB compared with 16.1% of those with NPTB (5 of 31) (Chi2: p=0.062). In the three-group analysis, 41.0%

of those with DPTB (16 of 39) reported chronic bronchitis, 26.5% with PrPTB (9 of 34) and 16.1% with NPTB (Chi2: p=0.069) [see Table 56 and Table 57]

Table 56: Presence of chronic bronchitis according to PPTB status: NPTB vs. PPTB.

	NPTB	%	PPTB	%	*p-value*	*test*
No Chronic Bronchitis	26	83.9%	48	65.8%		
Chronic Bronchitis	5	16.1%	25	34.3%	*0.062*	*Chi2*
Total	31		73			

Table 57: Presence of chronic bronchitis according to PPTB status: three-group analysis.

	NPTB	%	DPTB	%	PrPTB	%	*p-value*	*test*
No Chronic Bronchitis	26	83.9%	23	59.0%	25	73.5%		
Chronic Bronchitis	5	16.1%	16	41.0%	9	26.5%	*0.069*	*Chi2*
TOTAL	31		39		34			

8.2.2. Physiology tests at Visit 2

For Visit 2, 103 subjects were able to perform spirometry. The following variables were not normally distributed and required analysis using non-parametric statistical tests:

- Post-bronchodilator FEV1 (litres)
- Post-bronchodilator FVC (litres)
- Post-bronchodilator FEV1:FVC.

Findings of Visit 2 data and analysis are presented in Table 58.

8.2.2.1. Post-bronchodilator FVC

There was no significant difference in the median post bronchodilator FVC (litres) between those with or without PPTB (Wilcoxon p=0.398). Similarly, no difference was found in the comparison of the three subgroups: NPTB, DPTB and PrPTB (Kruskal Wallis p=0.368).

There was also no difference in the mean post-bronchodilator FVC (as % predicted) between those with and without PPTB (Satterthwaite's t-test for

unequal variances p=0.917). No difference was found between the three subgroups (ANOVA p=0.990).

8.2.2.2. Post-bronchodilator FEV1

There was no significant difference in the median post-bronchodilator FEV1 (litres), between those with or without PPTB (Wilcoxon p=0.440), and no significant difference on three-group analysis of the NPTB, DPTB and PrPTB groups (Kruskal Wallis p=0.617).

FEV1 (% predicted) was both normally distributed and had equal variance. Thus, one sample t-test and ANOVA tests were used. The difference in the FEV1 (% predicted) between those with NPTB (mean FEV1 75.1%) and those with PPTB (mean FEV1 67.0%) was not significant (t-test p=0.090) [see Figure 43]. On three-group analysis, the difference between the NPTB (mean 75.1% predicted), DPTB (mean 63.0%) and PrPTB groups (mean 71.8%) was also not significant (ANOVA p=0.0529) [see Figure 44]. Using the Bonferroni correction, the difference between each pair of means was as follows:

- Difference between NPTB and DPTB: p=0.065
- Difference between NPTB and PrPTB: p=1.000
- Difference between DPTB and PrPTB: p=0.250.

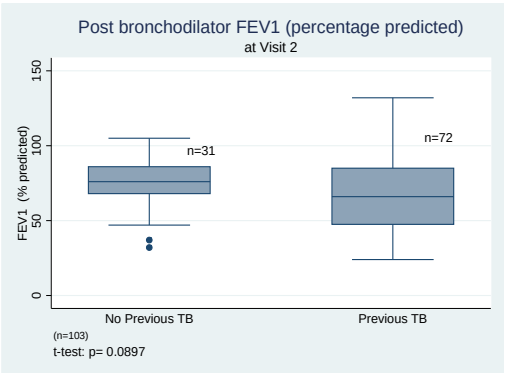


Figure 43: Post-bronchodilator FEV1 (% predicted) at Visit 2 according to PPTB status: NPTB vs. PPTB.

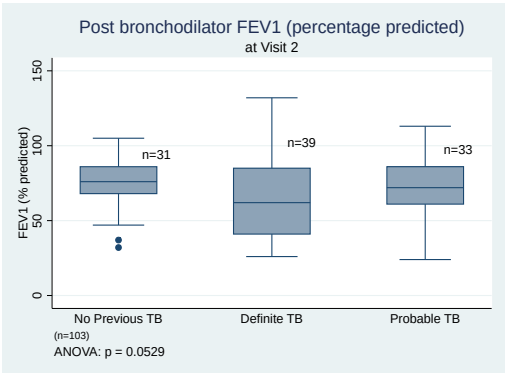


Figure 44: Post-bronchodilator FEV1 (% predicted) at Visit 2 according to PPTB status: three-group analysis.

Table 58: Comparison of the results of lung physiology at Visit 2 according to previous PTB status: PPTB vs. NPTB and by subgroups.

	NPTB	sd	PPTB	sd	*p-value*	*test*	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
(n)	(31)		(72)				(31)		(39)		(33)			
Post BD FVC (L) - mean	2.76	0.849	3.00	1.051	*n/a*		2.76	0.849	3.11	1.049	2.87	1.053	*n/a*	
Post BD FVC (L) - median	2.80	-	2.83	-	*0.398*	*Wilcoxon*	2.80	-	3.22	-	2.65	-	*0.368*	*Kwallis*
Post BD FVC (%) - mean	96.29	11.335	95.99	17.490	*0.917*	*Satterthwaite t-test*	96.29	11.335	95.79	19.195	96.21	15, 532	*0.990*	*ANOVA*
Post BD FEV1 (L) -mean	1.74	0.638	1.67	0.746	*n/a*	*n/a*	1.74	0.638	1.64	0.797	1.70	0.693	*n/a*	*n/a*
Post BD FEV1 (L) - median	1.68	-	1.44	-	*0.440*	*Wilcoxon*	1.68	-	1.41	-	1.49	-	*0.617*	*Kwallis*
Post BD FEV1 (%) -mean	75.06	18.282	67.04	23.126	*0.090*	*t-test*	75.06	18.282	62.95	24.880	71.88	20.172	*0.053*	*ANOVA*
Post BD FEV1:FVC - mean	0.63	0.131	0.56	0.141	*n/a*	*n/a*	0.63	0.131	0.52	0.133	0.60	0.138	*n/a*	*n/a*
Post BD FEV1:FVC - median	0.67	-	0.60	-	*0.012*	*Wilcoxon*	0.67	-	0.54	-	0.63	-	*0.002*	*Kwallis*
Reversibility														
Litres - median	0.20	0.156	0.19	0.168	*0.730*	*Wilcoxon*	0.20	0.16	0.16	0.148	0.19	0.190	*0.879*	*Kwallis*
% change	11.76	13.708	11.99	16.708	*0.994*	*Wilcoxon*	11.76	13.71	11.77	18.148	12.63	15.106	*1.000*	*Kwallis*
Significant reversibility*														
Number of subjects	13	-	26	-			13	-	12	-	14	-		
%	(0.42)	-	(0.36)	-	*0.576*	*Chi2*	0.42	-	0.31	-	0.42	-	*0.511*	*Chi2*
DLCO (mL/min/mmHg)	18.06	5.483	15.16	4.954	*0.010*	*t-test*	18.06	5.483	14.93	4.754	15.44	5.242	*0.033*	*ANOVA*
DLCO (%)	79.52	23.659	64.85	19.553	*0.002*	*t-test*	79.52	23.659	61.72	15.285	68.55	23.341	*0.003*	*ANOVA*
***Significant reversibility = change in FEV1 of >200mL & >12%*														

8.2.2.3. Rate of decline in FEV1

The rate of decline in FEV1 between the BOLD 2005 study and Visit 1 spirometry of the Follow-up study (2010) are presented in **Table 60**. No difference in either the absolute decline in FEV1 or the rate of decline was found between subjects with and without PPTB. The FEV1 declined by a median of 119 mL (16.8 mL/yr) in those with NPTB and by 170 mL (32.7 mL/yr) in those with PPTB (Wilcoxon p=0.283). There was also no difference in the rate of decline between the subgroups.

8.2.2.4. FEV1:FVC

The median FEV1:FVC was significantly lower in subjects with PPTB (median ratio 0.60) compared with those subjects with NPTB (median ratio 0.67) (Wilcoxon p=0.012) [see Figure 45].

Additionally, on three-group analysis, there was a significant difference in median FEV1:FVC between those with NPTB (median ratio 0.67), those with DPTB (median ratio 0.54) and those with PrPTB (median ratio 0.63) (Kruskal-Wallis Test p=0.002) [see Figure 46].

Comparing the median FEV1:FVC between the individual groups using the Wilcoxon test yielded the following results:

- Difference between NPTB and DPTB: p=0.0006
- Difference between NPTB and PrPTB: p=0.4011
- Difference between DPTB and PrPTB: p=0.0098.

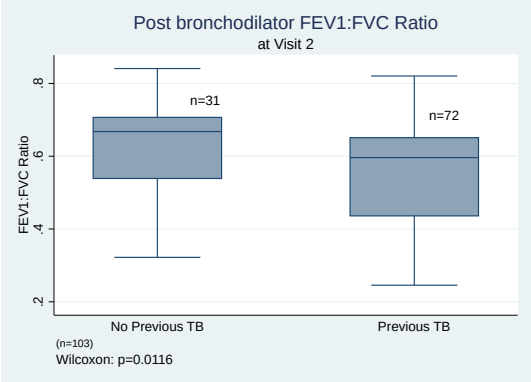


Figure 45: Post-bronchodilator FEV1:FVC at Visit 2 according to PPTB status, NPTB vs. PPTB.

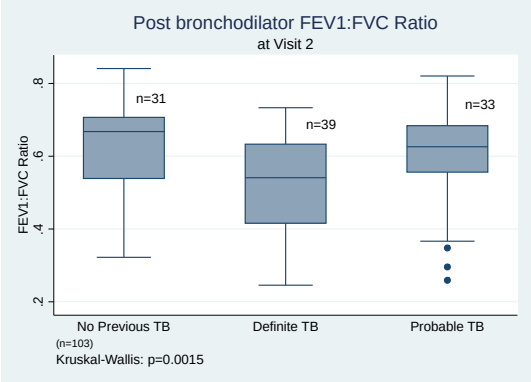


Figure 46: Post-bronchodilator FEV1:FVC at Visit 2 according to PPTB status: three-group analysis.

8.2.2.4. Bronchodilator responsiveness

Bronchodilator responses (change in FEV1 45 minutes after administration of 400 µg salbutamol and 80 µg ipratropium bromide anhydrous) were similar in those with and without PPTB, whether expressed in litres or percentage change. Additionally, there was no significant difference when three-group analysis was performed. Neither was there a difference in the proportion of subjects with significant reversibility (defined as a change in FEV1 of more than 200 mL and 12.0%) between subjects with and without PPTB, or in three-group analysis [see Table 58].

8.2.2.5. Diffusing capacity (DL_{CO})

A significantly higher mean DL_{CO} (ml/min/mmHg) was found in subjects with NPTB (18.06 mL/min/mmHg, sd=5.483) compared with PPTB (15.16 mL/min/mmHg, sd=4.954) (t-test p=0.0097) [see Figure 47]. The difference between DPTB (14.93 mL/min/mmHg, sd=4.754), PrPTB (15.44 mL/min/mmHg, sd=5.242) and NPTB groups (18.06 mL/min/mmHg, sd=5.483) was also significant (ANOVA p=0.003) [see Figure 48]. However, on Bonferroni correction only the difference between those with NPTB and DPTB remained (p=0.033).

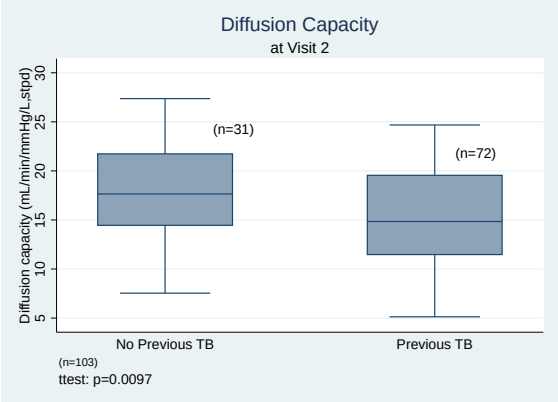


Figure 47: Diffusing capacity (mLl/min/mmHg) according to PPTB status : NPTB vs. PPTB.

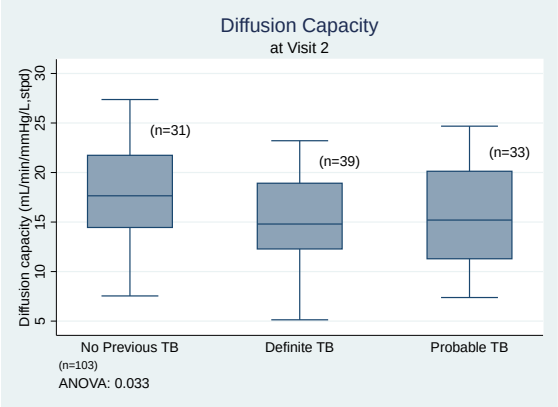


Figure 48: Diffusing capacity (mL/min/mmHg) according to PPTB status: three-group analysis.

DL_{CO}, expressed as percentage of predicted, was also higher in subjects with NPTB (79.5%, sd=23.7%) vs. those with PPTB (64.9%, sd=19.6%) (t-test p=0.002) [see Figure 49]. It was also significantly different in three-group analysis between those with NPTB (79.5%, sd=23.7%), DPTB (61.7%, sd=15.3%) and PrPTB (68.6%, sd=23.3%) (ANOVA p=0.003) [see Figure 50]. The Bonferroni correction confirmed a significant difference only between those with NPTB and those with DPTB (p=0.002).

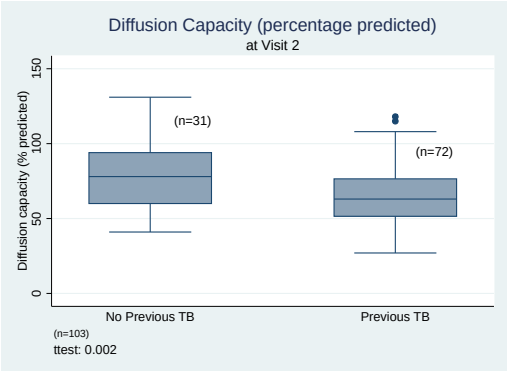


Figure 49: Diffusing capacity (%predicted) according to PPTB status: NPTB vs. PPTB.

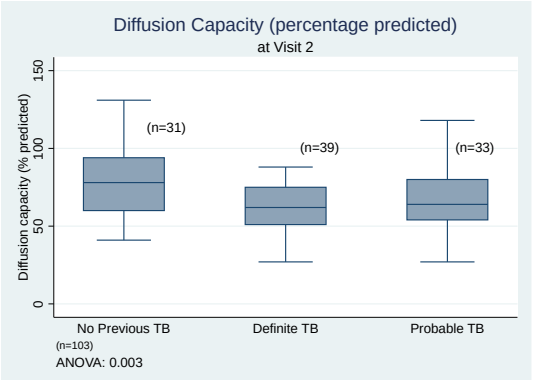


Figure 50: Diffusing capacity (%predicted) according to PPTB status: three-group analysis.

8.2.3. Lung physiology tests at Visit 3

The mean time interval between Visit 2 and 3 was 16.4 days (median 15 days, sd=3.605 days, min 11 days, max 29 days). The result of the spirometry on 103 subjects tested at Visit 3 is presented in Table 59.

8.2.3.1. Post-bronchodilator FVC

There was no significant difference in the medians of FVC (litres) at Visit 3 between those with PPTB and those without (Wilcoxon p=0.256). Moreover, there was no significant difference between the three groups (NPTB, DPTB and PrPTB) in the median FVC (litres) at Visit 3 (Kruskal-Wallis p=0.309).

Similarly, values for FVC expressed as percentage of predicted between those with and without PPTB were not significantly different (Wilcoxon p=0.846) (three-group analysis, Kruskal-Wallis p=0.954).

8.2.3.2. Post-bronchodilator FEV1

There was no significant difference in the median FEV1 (liters) at Visit 3 between those with PPTB and those without (Wilcoxon p=0.421). Additionally, there was no significant difference in the median FEV1 (litres) on three-group analysis (Kruskal-Wallis p=0.522).

Similarly, values for FEV1 expressed as percentage of predicted were not significantly different between those with and without PPTB (t-test p=0.159), nor on three-group analysis (ANOVA p=0.058). Application of the Bonferroni correction confirmed no significant difference between the three groups.

8.2.3.3. FEV1:FVC

FEV1:FVC (a non-parametric variable) was significantly lower in subjects with PPTB (median ratio 60.9%) compared to those with NPTB (median ratio 65.4%) (Wilcoxon p=0.021) [see Figure 51]. Additionally, on subgroup analysis, there was a significant difference in the median FEV1:FVC between those with NPTB (median ratio 65.4%), DPTB (median ratio 54.6%) and PrPTB (median ratio 62.1%) (Kruskal-Wallis p=0.002) [see Figure 52].

Comparing the median FEV1:FVC between the individual groups using the Wilcoxon test yielded the following results:

- Difference between NPTB and DPTB: p=0.0012
- Difference between NPTB and PrPTB: p=0.5278
- Difference between DPTB and PrPTB: p=0.0066.

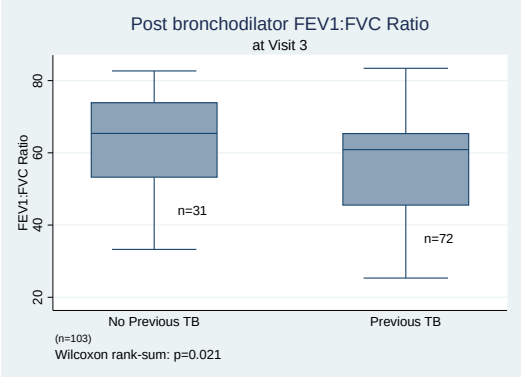


Figure 51: FEV1:FVC by PPTB status at Visit 3: NPTB vs. PPTB.

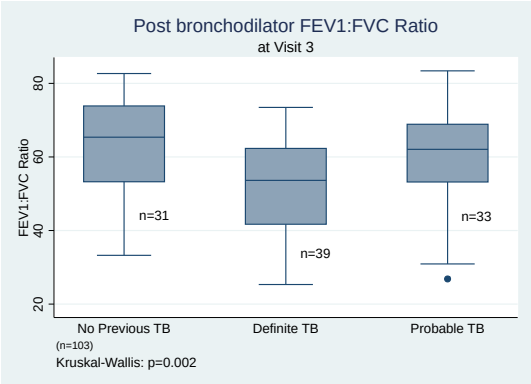


Figure 52: FEV1:FVC by PPTB status at Visit 3: three-group analysis.

Table 59: Comparison of results of lung physiology at Visit 3 according to previous PTB status: PPTB vs. NPTB and by subgroups.

(n = 103)	NPTB	sd	PPTB	sd	*p-value*	*test*	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
(n)	(31)		(72)				(31)		(39)		(33)			
Post BD FVC (L) -mean	2.75	0.890	3.05	1.086	*n/a*	*n/a*	2.75	0.890	3.14	1.062	2.95	1.121	*n/a*	*n/a*
Post BD FVC (L) -median	2.61	-	2.89	-	*0.256*	*Wilcoxon*	2.61	-	3.05	-	2.64	-	*0.309*	*Kwallis*
Post BD FVC (%) - mean	95.65	16.881	97.25	18.646	*n/a*	*n/a*	95.65	16.881	96.67	19.130	97.94	18.328	*n/a*	*n/a*
Post BD FVC (%) - median	95		97		*0.846*	*Wilcoxon*	95		97	-	98	-	*0.954*	*Kwallis*
Post BD FEV1 (L) -mean	1.73	0.632	1.69	0.754	*n/a*	*n/a*	1.73	0.632	1.66	0.787	1.74	0.723	*n/a*	*n/a*
Post BD FEV1 (L) - median	1.71	-	1.38	-	*0.421*	*Wilcoxon*	1.71	-	1.36	-	1.55		*0.522*	*Kwallis*
Post BD FEV1 (%) -mean	75.03	22.016	67.52	25.679	*0.159*	*t-test*	75.03	22.016	62.40	27.074	73.58	22.865	*0.058*	*ANOVA*
Post BD FEV1:FVC - mean	63.12	12.992	55.84	14.086	*n/a*	*n/a*	63.12	12.992	51.87	13.004	60.52	14.058	*n/a*	*n/a*
Post BD FEV1:FVC - median	65.37	-	60.89	-	*0.021*	*Wilcoxon*	65.37	-	53.63	-	62.07	-	*0.002*	*Kwallis*

Table 60: Rate of decline in FEV1 between BOLD 2005 and Follow-up studies, according to PPTB status (using Visit 1 data).

(n = 103)	NPTB	sd	Prev TB	sd	*Test*	NPTB	sd	DPTB	sd	PrPTB	sd	*Test*
(n)	(30)		(73)			(30)		(39)		(34)		
Change in FEV1 (mL)												
mean	-119	201	-160	367	*p=0.283*	-119	201	-139	432	-183	278	*p=0.561*
median	-95		-170		*(Wilcoxon)*	-95		-170		-165		*(Kwallis)*
Rate of Change (mL per year)												
mean	-22.5	37.8	-30.3	67.5	*p=0.273*	-22.6	37.8	-26.4	77.9	-34.7	54.1	*p=0.545*
median	-16.8		-32.7		*Wilcoxon)*	-16.8		-34.3		-31.2		*(Kwallis)*

8.2.3.4. Whole body plethysmography

Of the 104 subjects with Visit 3 data, four were unable to perform reproducible manoeuvres and one subject was older than 80 years, for whom no ECCS predicted values are available; these five subjects were excluded. The results for the remaining subjects are presented in **Table 61**

There was no significant difference between subjects with and without PPTB for the following volumes:

- Total Lung Capacity (TLC) - in litres and as a percentage of predicted.
- Vital Capacity (VC) – in litres and as a percentage of predicted values.

Similarly, on three-group analysis, there was no significant difference in TLC or VC between subjects with DPTB, PPTB and NPTB.

Mean inspiratory capacity (IC in litres) was significantly lower in subjects with PPTB compared to those with NPTB (2.04 L vs. 2.40 L, t-test p=0.006). Additionally, a significantly lower median percentage-predicted IC was found in those with PPTB (93% vs. 120%, Wilcoxon p<0.0001). Analysis of the three subgroups confirmed significantly lower IC in subjects with DPTB (mean 2.03 L, median 92% pred) and PrPTB (mean 2.06 L, median 99.5% pred) compared to subjects with NPTB (mean 2.40 L, median 120% pred) [see **Table 61**].

Functional residual capacity (FRC in litres) was significantly higher in subjects with PPTB compared to those without (median 3.45 L vs. 2.78 L, Wilcoxon p=0.0018), with the median percentage predicted FRC also significantly higher (median 116% vs. 103%, Wilcoxon p=0.0022). Three-group analysis confirmed higher values for FRC in both DPTB (median 3.72 L, median 121.5% pred) and PrPTB groups (median 2.93 L, median 110.0% pred) compared with subjects in the NPTB group (median 2.78 L, median 103% pred).

Similarly, the expiratory reserve volume (ERV in litres and as percentage of predicted) was higher in subjects with PPTB compared to those with NPTB (median 0.57 L vs. 0.19 L, Wilcoxon p=0.0001, and 63.5% vs. 22%, Wilcoxon p<0.0001, respectively). The ERV was also higher in subjects with DPTB (median 0.685 L, median 73% pred) and PrPTB (median

0.445 L, median 51.5% pred) than in subjects with NPTB (median 0.19 L, median 22% pred). Residual Volume (RV in litres) was higher in subjects with PPTB than in those without (median 2.785 L vs. 2.49L, Wilcoxon p=0.0517), but not when expressed as a percentage of predicted (median 133.5% vs. 133%, Wilcoxon p=0.244). Similarly, in three-group analysis, the significant difference in the RV expressed in litres was not found when expressed as a percentage predicted.

Values for RV:TLC between subjects with and without PPTB were not found to be significantly different (mean 0.54 vs. 0.51, t-test p=0.0598). Similarly, values for the three subgroups were not significantly different (ANOVA p=0.1093).

Table 61: Comparison of results of whole body plethysmography at Visit 3 according to previous TB status: PPTB vs. NPTB and by subgroups

(n=99)	NPTB	sd	PPTB	sd	*p-value*	*test*	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
(n)	(29)		(70)				(29)		(38)		(32)			
TLC (L)- mean*	5.40	1.250	5.800	1.519	*0.2074*	*t-test*	5.40	1.250	6.02	1.350	5.54	1.683	*n/a*	*n/a*
TLC (L)- median	5.43	-	5.615	-	*n/a*	*n/a*	5.43#	-	5.97#	-	4.74#	-	*0.0943*	*Kwallis*
TLC (%)- mean#	102.9	15.18	105.2	18.47	*n/a*	*n/a*	102.9	15.18	107.4	21.03	102.5	14.77	*n/a*	*n/a*
TLC (%)- median	102		102.5	-	*0.6555*	*Wilcoxon*	102		102	-	103	-	*0.795*	*Kwallis*
VC (L)- mean#	2.70	0.691	2.72	0.885	*n/a*	*n/a*	2.70	0.691	2.77	0.874	2.66	0.907	*n/a*	*n/a*
VC (L)- median	2.74	-	2.64	-	*0.8717*	*Wilcoxon*	2.74	-	2.77	-	2.5	-	*0.8531*	*Kwallis*
VC (%)- mean*	88.97	12.724	83.73	14.411	*0.0922*	*t-test*	88.97	12.724	81.89	13.830	85.91	14.998	*0.1192*	*ANOVA*
VC (%)- median	90	-	85	-	*n/a*	*n/a*	90	-	84	-	88		*n/a*	*n/a*
IC (L)- mean*	2.40	0.544	2.04	0.589	*0.0064*	*t-test*	2.40	0.544	2.03	0.521	2.06	0.669	*0.024*	*ANOVA*
IC (L)- median	2.39	-	2.05	-	*n/a*	*n/a*	2.39	-	2.075	-	2.035	-	*n/a*	*n/a*
IC (%)- mean#	119.1	21.51	96.2	27.36	*n/a*	*n/a*	119.1	21.51	93.1	29.00	99.8	25.23	*n/a*	*n/a*
IC (%)- median	120	-	93	-	*<0.0001*	*Wilcoxon*	120	-	92	-	99.5	-	*0.0001*	*Kwallis*
FRC (L)- mean#	2.96	0.913	3.76	1.230	*n/a*	*n/a*	2.96	0.913	3.99	1.139	3.48	1.293	*n/a*	*n/a*
FRC (L)- median	2.78	-	3.45	-	*0.0018*	*Wilcoxon*	2.78	-	3.72	-	2.925	-	*0.0005*	*Kwallis*
FRC (%)- mean#	103.5	27.00	124.2	32.91	*n/a*	*n/a*	103.5	27.00	130.5	35.02	116.8	28.99	*n/a*	*n/a*
FRC (%)- median	103	-	116	-	*0.0022*	*Wilcoxon*	103	-	121.5	-	110	-	*0.002*	*Kwallis*

(n=99)	NPTB	sd	PPTB	sd	*p-value*	*test*	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
(n)	**(29)**		**(70)**				**(29)**		**(38)**		**(32)**			
ERV (L)- mean#	0.31	0.314	0.68	0.510	*n/a*	*n/a*	0.31	0.314	0.75	0.510	0.6	0.506	*n/a*	*n/a*
ERV (L)- median	0.19	-	0.57	-	*0.0001*	*Wilcoxon*	0.19	-	0.685		0.445	-	*0.0002*	*Kwallis*
ERV (%)- mean#	33.5	26.82	70.1	43.58	*n/a*	*n/a*	33.5	26.82	73.0	41.69	66.8	46.16	*n/a*	*n/a*
ERV (%)- median	22	-	63.5	-	*<0.0001*	*Wilcoxon*	22	-	73		51.5	-	*0.0001*	*Kwallis*
RV (L)- mean#	2.69	0.782	3.08	0.988	*n/a*	*n/a*	2.69	0.782	3.25	1.000	2.88	0.952	*n/a*	*n/a*
RV (L)- median	2.49	-	2.785	-	*0.0517*	*Wilcoxon*	2.49	-	2.995	-	2.555	-	*0.0234*	*Kwallis*
RV (%)- mean#	134.6	34.11	148.5	48.47	*n/a*	*n/a*	134.6	34.11	156.9	55.56	138.6	36.84	*n/a*	*n/a*
RV (%)- median	133	-	133.5	-	*0.244*	*Wilcoxon*	133	-	139	-	130.5	-	*0.2478*	*Kwallis*
RV:TLC – mean*	49.7	6.62	53.1	8.62	*0.0598*	*t-test*	49.7	6.62	54.0	10.04	52.1	6.56	*0.1093*	*ANOVA*
RV:TLC - median	51	-	53.5		*n/a*	*n/a*	51	-	55.5		51.5	-	*0.1606*	*Kwallis*
	(n=28)		**(n=70)**				**(n=28)**		**(n=38)**		**(n=32)**			
TV – mean#	0.65	0.211	0.74	0.323			0.65	0.211	0.70	0.208	0.8	0.418	-	-
TV- median	0.65	-	0.67				0.65	-	0.68	-	0.665		-	-

** Parametric data*
 # Non-parametric data

8.2.4. Response to two-week trial of oral glucocorticosteroid and long acting B-agonist

8.2.4.1. Trial medication usage

The trial medication usage is described on page 70. Of the 103 subjects with spirometry at Visit 3, seven (6.8%) were not given prednisone for medical reasons: five had diabetes mellitus, one had poorly controlled hypertension, and one had a recent history of anaemia and GIT symptoms. Thus, 96 (93.2%) subjects received prednisone. The usage and duration of treatment are summarised in the Table 62 below. Of the 103 subjects, only two were not issued with formoterol (for medical reasons), while an additional five subjects reported non-use of formoterol (two because it caused dizziness; three gave no reason). Ninety-six subjects (93.2%) claimed compliance with formoterol use [see Table 62].

Table 62: Trial medication use and adherence between Visits 2 and 3.

	Prednisone	**Formoterol**
Subjects given medication	n=96 (93.2%)	n=101 (98.1%)
Subjects not given medication	n=7 (6.8%)	n=2 (1.9%)
Days between visits	(n=96)	
Mean	16.25	
SD	3.45	
Min-Max	(13 - 29)	
Tablets used		
Unknown (n)	n=8 (8.3%)	n/a
Known (n)	n=88 (91.7%)	n/a
Mean number of tablets used	55.67	n/a
SD	19.32	n/a
Min-Max	(7 - 108)	n/a
Percentage compliance*		
(Adherence unknown)	n=8 (8.3%)	n=0 (0%)
Adherence known	n=88 (91.7%)	n=96 (93.2%)
Mean percentage adherence(%)	87.50	n/a
SD (%)	26.94	n/a
Min-Max (%)	(12 - 133)	n/a
n >75% adherence	n=68	
n > 80% adherence	n=65	

**Percentage adherence= (number of tablets taken)÷(number of tablets prescribed)*

8.2.4.2. Changes in spirometry between Visit 2 and 3

In order to eliminate the effect of poor adherence, the analysis was limited to subjects with more than 75% adherence to prednisone treatment, which was 68 subjects.

Overall, the median improvement in pre-bronchodilator FEV1 from baseline after the two-week trial of prednisone and formoterol was 70 mL for subjects with PPTB (110 mL for DPTB and 60 mL for PrPTB) and 90 mL for NPTB.

Comparing the NPTB and PPTB groups, there was no significant difference in any of the following measures [see Table 63]:

- Pre-bronchodilator FEV1 (litres and % predicted)
- Post-bronchodilator FEV1 (litres and % predicted)
- Pre-bronchodilator FVC
- Post-bronchodilator FVC
- FEV1:FVC (both pre- and post-bronchodilator).

Additionally, there was no significant difference in the above variables on three-group analysis (i.e. DPTB, PrPTB and NPTB) [see Table 64].

When the above analysis was performed using all subjects who were prescribed prednisone and formoterol, no difference was found between groups or subgroups – regardless of adherence (n=92).

Table 63: Change in spirometry after two-week medication trial, in subjects with greater than 75% adherence.

	All subjects	**sd**	**NPTB**	**sd**	**PPTB**	**sd**	***p-value***	***Test****
(n)	(68)		(16)		(52)			
Change in PreBD FEV1								
litres: mean (median)	0.118 (0.08)	0.222	0.138 (0.09)	0.278	0.112 (0.07)	0.205	*0.79*	*Wilcoxon*
% predicted: mean (median)	4.67 (2.5)	12.985	8.06 (4)	20.111	3.625 (2)	9.890	*0.94*	*Wilcoxon*
Change in Post BD FEV1								
litres: mean (median)	0.031 (0.04)	0.239	0.0088 (-0.025)	0.353	0.038 (0.055)	0.195	*0.52*	*Wilcoxon*
% predicted: mean (median)	1.56 (1.5)	13.121	0.625 (-1)	22.671	1.846 (2)	8.640	*0.35*	*Wilcoxon*
Change in PreBD FVC								
litres: mean (median)	0.157 (0.105)	0.327	0.159 (0.07)	0.384	0.156 (0.12)	0.311	*0.74*	*Wilcoxon*

	All subjects	sd	NPTB	sd	PPTB	sd	*p-value*	*Test**
Change in PostBD FVC								
litres: mean (median)	0.0587 (0.06)	0.354	0.0463 (0.03)	0.530	0.0625 (0.06)	0.286	*0.62*	*Wilcoxon*
Change in PreBD FEV1:FVC								
litres: mean (median)	0.0128 (0.0113)	0.044	0.0199 (0.00974)	0.050	0.0106 (0.0113)	0.04	*0.82*	*Wilcoxon*
Change in PostBD FEV1:FVC								
litres: mean (median)	0.00234 (0.00137)	0.045	-0.00611 (-0.00136)	0.054	0.00494 (0.00231)	0.04	*0.82*	*Wilcoxon*

**All variable measured were non-parametrically distributed*
BD = bronchodilator

Table 64: Change in spirometry after two-week medication trial in subjects with greater than 75% adherence: three-group analysis.

	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*Test**
(n)	(16)		(27)		(25)			
Change in PreBD FEV1								
litres: mean (median)	0.138 (0.09)	0.278	0.0874 (0.11)	0.193	0.139 (0.06)	0.218	*0.919*	*Kwallis*
% predicted:mean (median)	8.06 (4)	20.111	1.723 (2)	10.959	5.68 (2)	8.325	*0.689*	*Kwallis*
Change in Post BD FEV1								
litres	0.0088 (-0.025)	0.353	0.0130 (0.05)	0.184	0.065 (0.06)	0.207	*0.713*	*Kwallis*
%	0.625 (-1)	22.671	0.926 (1)	8.241	2.84 (3)	9.114	*0.568*	*Kwallis*
Change in PreBD FVC								
litres: mean (median)	0.159 (0.07)	0.384	0.130 (0.13)	0.29	0.185 (0.1)	0.339	*0.924*	*Kwallis*
Change in PostBD FVC								
litres: mean (median)	0.0463 (0.03)	0.530	0.0133 (-0.02)	0.25	0.116 (0.08)	0.316	*0.684*	*Kwallis*
Change in PreBD FEV1:FVC								
litres: mean (median)	0.0199 (0.00974)	0.050	0.00350 (-0.00429)	0.05	0.0183 (0.0200)	0.0299	*0.246*	*Kwallis*
Change in PostBD FEV1:FVC								
litres: mean (median)	-0.00611 (-0.00136)	0.054	0.00517 (-0.00054)	0.05	0.00468 (0.00626)	0.0328	*0.528*	*Kwallis*

**All variable measured were non-parametrically distributed*
BD = bronchodilator

8.2.4.3. MRC Dyspnoea score at Visits 2 and 3

Self-reported dyspnoea (MRC Dyspnoea score) was recorded before and after the two-week medication trial (i.e. Visits 2 and 3, respectively).

There were no significant differences between the groups or subgroups in MRC Dyspnoea scores at either Visit 2 or Visit 3 [Visit 2 MRC Dyspnoea scores presented in Table 65]. Additionally, there was no significant difference between the groups in the change in MRC Dyspnoea

score between visits [see Table 66]. No difference between the groups, regarding change in MRC score, was observed when analysis was restricted to subjects with >75% adherence with medication trial (Wilcoxon p=0.330, Kruskal-Wallis p=0.585).

Table 65: Baseline MRC Dyspnoea scores at commencement of two-week trial of medication (Visit 2).

	All	NPTB	PPTB	p-value	NPTB	DPTB	PrPTB	p-value
(n)	**(102)**	**(31)**	**(71)**		**(31)**	**(38)**	**(33)**	
Average MRC score								
Mean	**2.93**	2.87	2.96		2.87	3.03	2.88	0.547 ANOVA
Median	**2.5**	2.00	3.00	0.842 Wilcoxon	2.00	3.00	2.00	
Number of subjects in MRC group								
MRC 1	**21**	6	15		6	5	10	
MRC 2	**30**	10	20		10	12	8	
MRC 3	**15**	5	10		5	8	2	
MRC 4	**7**	2	5		2	3	2	
MRC 5	**29**	8	21		8	10	11	
Total	**102**	31	71	0.792 Chi2 (for trends)	31	38	33	0.770 Kwallis

Table 66: Change in MRC Dyspnoea score after two-week medication trial.

	All	NPTB	Prev TB	p-value	NPTB	DPTB	PrPTB	p-value
(n)	**(102)**	(31)	(71)		(31)	(38)	(33)	
Mean	-0.52	-0.48	-0.54		-0.48	-0.45	-0.64	0.961 Kwallis
Median	0	0	0	0.818 Wilcoxon	0	0	0	

8.2.5. St George's Respiratory questionnaire

The Subjects' baseline symptoms and performance status were assessed at their first visit (Visit 1) using the St George's Respiratory Questionnaire (SGRQ) [see Appendix 3 - St George's Respiratory Questionnaire]. The median total score was 34.6 and 32.6 for subjects with and without PPTB, respectively. These values exceed the total scores for healthy adults, which range from 5 to 7. No difference in the Symptom, Activity or Total SGRQ scores was found between PPTB and NPTB [see Table 67]; however, there

was a trend towards worse symptoms (a higher score) in the Impact Domain of subjects with PPTB (Wilcoxon p=0.076). Analysis of subgroups revealed no significant between-group differences for any of the SGRQ domains [see Table 67].

Table 67: St George's Respiratory Questionnaire (SGRQ) scores according to PPTB status.

	NPTB	sd	PPTB	sd	*p-value*	*Test**	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*Test**
Symptom Score (n)	(31)		(72)				(31)		(38)		(34)			
Mean	37.15	24.783	28.59	25.518	*n/a*	*n/a*	37.15	24.783	37.16	24.317	40.19	27.074	*n/a*	*n/a*
Median	42.27	-	37.59	-	*0.714*	*Wilcoxon*	42.27	-	33.69	-	43.16	-	*0.836*	*Kwallis*
Activity Score (n)	(31)		(72)				(31)		(38)		(34)			
Mean	48.92	30.496	49.39	31.441	*n/a*	*n/a*	48.92	30.496	50.90	30.174	47.69	33.172	*n/a*	*n/a*
Median	59.457	-	53.62	-	*0.888*	*Wilcoxon*	59.457	-	56.54	-	53.57	-	*0.944*	*Kwallis*
Impact Score (n)	(31)		(70)				(31)		(36)		(34)			
Mean	17.50	15.663	28.20	25.713	*n/a*	*n/a*	17.50	15.663	27.86	23.473	28.57	28.246	*n/a*	*n/a*
Median	16.52	-	21.12	-	*0.076*	*Wilcoxon*	16.52	-	21.12	-	20.68	-	*0.199*	*Kwallis*
Total Score (n)	(31)		(70)				(31)		(36)		(34)			
Mean	30.62	20.478	36.75	25.693	*n/a*	*n/a*	30.62	20.478	36.87	24.176	36.61	27.574	*n/a*	*n/a*
Median	32.60	-	34.59	-	*0.324*	*Wilcoxon*	32.60	-	34.59	-	35.09	-	*0.607*	*Kwallis*

**** All variable were non parametrically distributed***
 # St George's Respiratory Questionnaire - performed at Visit 1

8.3. Analysis of subjects with chronic airflow obstruction only

As a sensitivity analysis, the analysis of group and subgroup differences in lung function tests was performed including only subjects in whom CAO was confirmed on post-bronchodilator spirometry at Visit 2. Seventeen of 103 subjects (16.5%) were excluded on this basis: nine from the NPTB (29.0%), seven from the PrPTB (21.2%), and one from the DPTB group (2.5%). Thereafter, results from 86 (83.5%) of the full cohort were analysed. Of those analysed, 22 (25.6%) were classified as NPTB, 38 (44.2%) as DPTB and 26 (32.7%) as PrPTB.

The results of this further analysis were similar to those for the full cohort. These results are presented in Appendix 7 – Results of Clinical and Physiological Endpoints only for Subjects with Chronic Airflow Obstruction. Only the post-bronchodilator FEV1:FVC, which was previously noted to be higher in subjects with NPTB, was no longer found to be statistically different in subjects with PPTB (Wilcoxon p=0.135).

The mean DL_{CO} (both as absolute values and % predicted) was significantly lower in subjects with PPTB compared to those without (t-test p=0.027 and p=0.005, respectively), including in three-group analysis of NPTB, DPTB and PrPTB (ANOVA p=0.0126).

Similarly, the inspiratory capacity was significantly lower in subjects with previous TB, compared to both subjects without previous TB (Wilcoxon p=0.0002), and in three-group analysis (Krusal-Wallis p=0.0004).

8.4. Summary of findings

Significantly more subjects with previous pulmonary TB reported being an ex- or current smoker, but this difference was not seen on three-way analysis between the subgroups: NPTB, DPTB and PrPTB. Additionally, there was no difference in the number of pack-years smoked between those with and without PPTB. Chronic bronchitis was not found to be more common in

subjects with PPTB, when both the full cohort and only those with CAO was assessed. Thus, there is lack of association between these two confounders and PPTB status.

Prior to the medication trial (Visit 2), the median FEV1:FVC was significantly lower in subjects with PPTB, and the FEV1 (% predicted) was numerically lower (borderline significance), but the FVC was similar. When subjects without CAO were excluded, no differences in FEV1:FVC, FEV1 or FVC between subjects with PPTB and NPTB were observed. This is likely due to over-representation of subjects without CAO in the NPTB group (29.0% of the NPTB group (9 of 31) did not have airflow obstruction, compared with 11.1% of the PPTB group (8 of 72), 2.5% of the DPTB group and 21.2% of the PrPTB group). Similarly, the lower FEV1:FVC observed at Visit 3 in subjects with PPTB was absent when subjects with no CAO were excluded from analysis.

The gains in pre-bronchodilator FEV1 after a two-week trial of prednisone and formoterol were small, being merely 70 mL for subjects with PPTB and 90 mL for NPTB. Importantly, there were no between-group differences in outcomes of FEV1, FVC, FEV1:FVC or MRC dyspnoea score after this short trial of medication.

Subjects with PPTB consistently showed a significantly lower DL_{CO} compared to subjects without PPTB, including on three-group analysis, with subjects in the DPTB group having a 17.8% lower DL_{CO} (% predicted) compared to subjects with NPTB.

Additionally, subjects with PPTB consistently showed a significantly lower inspiratory capacity (IC) than those without, as well as a higher functional residual capacity and Expiratory Reserve volume; there were no differences in the Total Lung Capacity, Vital Capacity and RV:TLC between those with and without PPTB. The median IC (% predicted) was 27.0% lower in subjects with PPTB.

There were no differences in baseline symptoms (MRC Dyspnoea score) and health status (SGRQ) between subjects with and without PPTB.

In the majority of three-group analyses, the PrPTB group was found to have values intermediate between those of the DPTB and NPTB groups, supporting the correct characterisation of subjects, described in the previous chapter.

Chapter 9. Results of Lung Imaging

9.1. Introduction

This chapter presents the results of the CT imaging performed on subjects in the BOLD cohort who were followed up in 2010. The purpose of the imaging was to improve the accuracy of clinical diagnosis, to confirm the presence of changes attributable to PPTB, and to examine differences in the relationships of structure (imaging findings) and function (lung function measurements) between subjects with and without a history of PPTB. The overall aim of these investigations was to establish whether there are grounds for considering tuberculosis-associated chronic obstructive pulmonary disease (TOPD) as a distinct phenotype of COPD.

The CT scans were performed at Visit 3, on the same day as whole body plethysmography, and quantitative analysis of the whole lung and all lobes as well as the bronchial tree was performed [see page 72].

As in the previous chapter, subjects were classified as having Previous Pulmonary TB (PPTB) – either Definite Previous TB (DPTB) or Probable Previous TB (PrPTB) - or No Previous TB (NPTB), as defined in Chapter 7.

9.2. Missing data

Chest CT scans were performed on 104 subjects, but in nine, the inspiratory images were unsuitable for analysis due to poor image quality, movement artifact and other technical reasons. One further scan was excluded due to previous right lobectomy for lung cancer. Two of the excluded subjects were in the NPTB group, four in the DPTB and three in the PrPTB groups.

The PPTB status of the remaining 94 scans are shown in Figure 53. Of these subjects, two did not have evaluable plethysmography data and 92 subjects had both analysable imaging and plethysmography data.

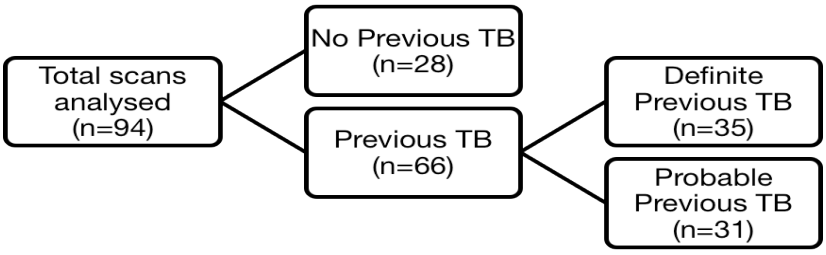


Figure 53: Classification of subjects according to PPTB status, for the analysis of CT scan images.

For technical reasons, quantification of residual volume scans was incomplete in a further three subjects. In two, the mean density scores for the right lung (right upper, middle and lower lobes) was missing, and in one, both these and the mean density scores for the left lower lobe were missing.

9.3. Imaging analysis of the full cohort

9.3.1. Lung volumes

9.3.1.1. Comparison with whole body plethysmography

There was strong correlation between total lung volumes measured by quantitative CT scan (at full inspiration) and plethysmography (Pairwise deletion correlation coefficient 0.9101, $p<0.0001$) [see Table 68, Table 69 and Figure 54].

Table 68: Comparison of total lung volume measurement by whole body plethysmography and quantitative CT scan in all subjects: NTPB vs. PPTB groups.

(volume in litres)	**All**	**sd**	**NPTB**	**sd**	**PPTB**	**sd**
(n)	(92)		(27)		(65)	
Plethysmography	5.71	1.440	5.50	1.223	5.81	1.152
(n)	(94)		(28)		(66)	
CT volume	5.15	1.467	4.91	1.189	5.24	1.568

Table 69: Comparison of total lung volume measurement by whole body plethysmography and quantitative CT scan: three-group analysis.

(volume in litres)	**NPTB**	**sd**	**DPTB**	**sd**	**PrPTB**	**sd**
(n)	(27)		(35)		(30)	
Plethysmography	5.50	1.223	5.94	1.376	5.65	1.677
(n)	(28)		(35)		(31)	
CT volume	4.91	1.189	5.32	1.505	5.16	1.658

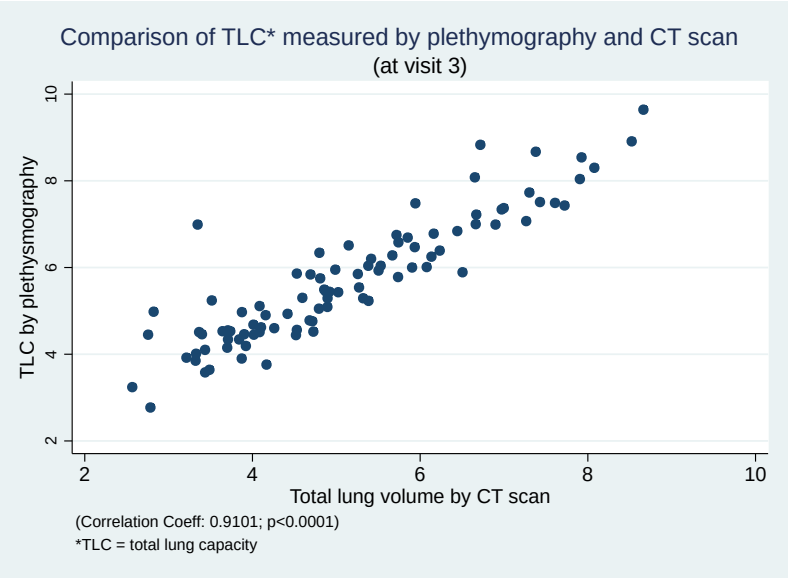


Figure 54: Comparison of total lung capacity measured by whole body plethysmography and CT scan.

9.3.1.2. Assessment of lobar volumes

A comparison was made of the each lung and lobe, expressed as a percentage of total lung volume at full inspiration (TLC) according to PPTB status. The total percentage volume occupied by the lower lobes, as well as that of the individual right and left lower lobes, was not significantly different between subjects with and without PPTB (Wilcoxon p=0.447, p=0.350 and p=0.785, respectively). Similarly, an analysis of volumes according to the three groups - DPTB, PrPTB and NPTB - revealed no differences (Kruskal-Wallis p=0.614 (both LL), p=0.632 (RLL) and ANOVA p=0.376 (LLL)) [see Table 70].

The median volume of the right upper lobe (RUL) (percentage of whole lung) was significantly lower in subjects with PPTB (20.7% vs. 22.6%, Wilcoxon p=0.035), than those with NPTB, but not when analysed according

to the three subgroups: DPTB (19.5%), PrPTB (21.9%) and NPTB (22.6%, Kruskal-Wallis p=0.107). However, a significantly lower median RUL volume was found, when subjects with DPTB were compared directly to those with NPTB, excluding subjects with PrPTB (Wilcoxon p=0.0332). In contrast, there was no significant difference left upper lobes (LUL) volumes of subjects with and without PPTB (Wilcoxon p=0.928), nor between the three subgroups (Kruskal-Wallis p=0.804).

Table 70: Comparison of lung and lobar volumes (as percentage of total lung volume) according to PPTB status.

(units = % of total lung volume)	**All**	**sd**	**NPTB**	**sd**	**PPTB**	**sd**	***p-value***	***test***	**NPTB**	**sd**	**DPTB**	sd	**PrPTB**	**sd**	***p-value***	***test***
(n)	(n=94)		(n=28)		(n=66)				(n=28)		(n=35)		(n=31)			
Lower Lobe Volume																
Total of both Lower Lobes #																
mean	47.32	7.321	45.84	6.044	47.96	7.755	*n/a*	*n/a*	45.84	6.044	48.79	9.424	47.03	5.288	*n/a*	*n/a*
median	46.76	-	46.96	-	46.28	-	*0.4469*	*WIlcoxon*	46.96	-	48.8	-	45.89	-	*0.6139*	*Kwallis*
RLL#																
mean	24.42	5.078	23.33	3.566	24.88	5.558	*n/a*	*n/a*	23.33	3.566	25.09	6.319	24.64	4.643	*n/a*	*n/a*
median	24.1	-	23.78	-	24.54	-	*0.3502*	*WIlcoxon*	23.78	-	24.85	-	24.14	-	*0.6318*	*Kwallis*
LLL#																
mean	22.91	4.183	22.51	3.495	23.08	4.457	*n/a*	*n/a*	22.51*	3.495	23.69*	5.290	22.38*	3.223	*0.3762*	*ANOVA*
median	22.52	-	22.4	-	22.5232	-	*0.785*	*WIlcoxon*	22.4	-	22.85	-	22.33	-	*0.6714*	*Kwallis*
Individual Lobes (%)	(n=94)		(n=28)		(n=66)				(n=28)		(n=35)		(n=31)			
RUL#																
mean	20.78	5.065	22.79	3.848	19.93	5.3	*n/a*	*n/a*	22.79	3.848	19.75	5.656	20.12	4.951	*n/a*	*n/a*
median	21.78	-	22.55	-	20.72	-	*0.035*	*WIlcoxon*	22.55	-	19.48	-	21.91	-	*0.1021*	*Kwallis*
RML*																
mean	7.77	2.660	7.14	2.062	8.04	2.849	*0.1368*	*t-test*	7.14	2.062	8.15	3.485	7.9	1.95	*0.3088*	*ANOVA*
median	7.63	-	6.97	-	8.14	-	*n/a*	*n/a*	6.97	-	8.04	-	8.19	-	*0.28*	*Kwallis*
LUL#																
mean	24.12	5.007	24.23	3.023	24.08	5.663	*n/a*	*n/a*	24.23	3.023	23.31	5.63	24.95	5.67	*n/a*	*n/a*
median	24.17	-	23.42	-	24.34	-	*0.9275*	*WIlcoxon*	23.42	-	24.3	-	24.37	-	*0.8041*	*Kwallis*

***Parametic variables**
***#Non-parametric variables**

9.3.2. Bronchial wall measurement

Use of the Pi10 as a measurement of bronchial wall thickness is described on page 54. The Pi10 is the square root of the wall area of a hypothetical bronchus with an internal perimeter of 10 mm, calculated from linear regression models and using data from all measured bronchi in the scan.

Two of the 104 scans were not analysed due to inability of the software algorithm to process these scans.

There was no significant difference in the median Pi10 values between subjects with and without PPTB (2.44 and 2.36, respectively, Wilcoxon p=0.87) [see Table 71]. Additionally, no significant difference in the Pi10 was found between those with DPTB (Pi10=2.35), PrPTB (Pi10=2.38) and NPTB (Pi10=2.44, Kruskal-Wallis p=0.76) [see Table 72].

Table 71: Bronchial wall area (Pi10) according to PPTB status: NPTB vs PPTB.

	All	**sd**	**NPTB**	**sd**	**PPTB**	**sd**	***p-value***	***test***
(n)	(102)		(30)		(72)			
Pi10								
Mean	2.45	0.56	2.46	0.55	2.44	0.57	*n/a*	*n/a*
Median	2.4		2.44		2.36		*0.87*	*Wilcoxon*

Table 72: Bronchial wall area (Pi10) according to PPTB status: three-group analysis.

(n=102)	**NPTB**	**sd**	**DPTB**	**sd**	**PrPTB**	**sd**	***p-value***	***test***
(n)	(30)		(39)		(33)			
Pi10								
Mean	2.46	0.55	2.44	0.64	2.45	0.48	n/a	n/a
Median	2.44		2.35		2.38		*0.76*	*Kwallis*

9.3.3. Lung density (average Hounsfield Units) measured at total lung capacity

The average density of the lungs was assessed at full inspiration (i.e. TLC).

The average (median) total density of the lungs was significantly lower in subjects with PPTB compared to subjects with NPTB (-852HU vs. -835HU; Wilcoxon p=0.04). Analysed according to the three subgroups this difference

was of borderline significance: DPTB -854HU, PrPTB -846HU and NPTB -835HU (Kruskal-Wallis: p=0.0666) [see Table 73].

The density scores were lower in subjects with PPTB than in those with NPTB for the following: Whole left lung (p=0.0505); whole right lung (p=0.0322); left lower lobe (LLL) (p=0.189); right middle lobe (RML) (p=0.006) and right lower lobe (RLL) (p=0.024). No differences in density in the right upper lobe (RUL) (p=0.298) and left upper lobes (LUL) (p=0.116) between subjects with PPTB and NPTB were observed [see Table 73].

On three-group comparison the following was found: a trend to lower densities for the whole left and right lungs (p=0.0596 and p=0.0654, respectively); and significantly lower densities for the LLL (p=0.0241), RML (p=0.0188) and RLL (0.0076) [see Table 73].

9.3.4. Lung density (average Hounsfield Unit) measured at residual volume

The mean density of both lungs (combined) measured at full expiration was significantly lower in subjects with PPTB compared to those without (–754HU vs. –701HU, t-test 0.0005), as well on three-group analysis: DPTB –762 HU, PrPTB –745 HU and NPTB –701 HU (ANOVA p=0.0014), when measured at full expiration [see **Table 74**].

The mean densities were significantly lower in subjects with PPTB for both left and right lungs (p=0.0019 and p=0.0003 respectively), as well as for all lobes individually. This finding was repeated on three-group analysis [see **Table 74**].

Table 73: Lung and lobar density (average Hounsfield Units - HU) at total lung capacity, according to PPTB status.

	All	sd	NPTB	sd	PPTB	sd	p-value (test)	NPTB	sd	DPTB	sd	PrPTB	sd	p-value (test)
(n)	(94)		(28)		(66)			(28)		(35)		(31)		
Total Lung#														
mean HU	-845.22	33.47	-833.7	35.3	-850.1	31.68	0.04 Wilcoxon	-833.7	35.3	-853.09	31.46	-846.74	32.1	0.0666 Kwallis
median HU	-848.44		-835.17		-851.95			-835.17		-853.77		-846.16		
Left Lung #														
mean HU	-844.96	36.47	-833.94	37.09	-849.64	35.46	0.0505 Wilcoxon	-833.94	37.09	-853.05	35.92	-845.78	35.12	0.0596 Kwallis
median HU	-850.43		-835.74		-853.42			-835.74		-859.64		-844.63		
LUL#														
mean HU	-849.04	38.15	-840.7	36.62	-852.58	38.51	0.1162 Wilcoxon	-840.7	36.62	-855.2	39.05	-849.63	38.32	0.1986 Kwallis
median HU	-855.95		-844.6		-858.23			-844.6		-857.64		-858.82		
LLL#														
mean HU	-838.42	38.38	-824.58	39.71	-844.29	36.54	0.0189 Wilcoxon	-824.58	39.71	-847.94	36.55	-840.17	36.68	0.0241 Kwallis
median HU	-844.33		-825.98		-848.64			-825.98		-851.69		-844.28		
Right Lung#														
mean HU	-845.24	32.13	-833.34	34.02	-850.28	30.17	0.0322 Wilcoxon	-833.34	34.02	-852.92	30.33	-847.31	30.19	0.0654 Kwallis
median HU	-849.75		-837.32		-853.51			-837.32		-854.94		-845.77		
RUL#														
mean HU	-846	32.75	-839.63	36.81	-848.69	30.78	0.2975 Wilcoxon	-839.63	36.81	-851.77	28.38	-845.23	33.42	0.5211 Kwallis
median HU	-850.48		-844.67		-853.15			-844.67		-851.23		-853.48		

	All	sd	NPTB	sd	PPTB	sd	p-value (test)	NPTB	sd	DPTB	sd	PrPTB	sd	p-value (test)
RML #														
mean HU	-856.75	31.9	-843.04	31.73	-862.57	30.37	0.006 t-test	-843.04*	31.73	-864.95*	31.25	-859.89*	29.63	0.0188 ANOVA
median HU	-857.65		-836.7		-864.61			-836.7		-865.66		-857.97		
RLL #														
mean HU	-837.36	40.73	-821.2	35.65	-844.22	41.06	0.024 Wilcoxon	-821.2	35.65	-845.2	45.79	-843.12	35.69	0.0076 Kwallis
median HU	-840.39		-824.62		-849.59			-824.62		-851.62		-843.32		

 # - nonparametric variables
**** -parametric variables***

Table 74: Lung and lobar density (average Hounsfield Units - HU) at residual volume, according to PPTB status.

	All	sd	NPTB	sd	PPTB	sd	p-value (test)	NPTB	sd	DPTB	sd	PrPTB	sd	p-value (test)
(n)	(94)		(28)		(66)			(28)		(35)		(31)		
Total Lung*														
mean HU	-738.61	69.032	-701.54	76.95	-754.33	59.29	0.0005 t-test	-701.54	76.95	-762.25	57.71	-745.39	60.72	0.0014 ANOVA
Left Lung *														
mean HU	-733.61	72.28	-698.75	75.97	-748.39	65.82	0.0019 t-test	-698.75	75.97	-755.89	66.27	-739.94	65.34	0.0054 ANOVA
LUL*														
mean HU	-751.15	73.36	-716.3	81.23	-765.94	64.92	0.0023 t-test	-716.3	81.23	-772.93	64.2	-758.04	65.86	0.0067 ANOVA
LLL#	***(n=93)***		***(n=27)***		***(n=66)***			***(n=27)***		***(n=35)***		***(n=31)***		
mean HU	-712.7	72.96	-682.9	69.18	-724.89	71.42	n/a	-682.9*	69.18	-732.89*	74.23	-715.85*	68.16	0.025 ANOVA
median HU	-706.86		-671.72		-712.67		0.0119 WIlcoxon							
Right Lung*	***(n=91)***		***(n=27)***		***(n=64)***			***(n=27)***		***(n=35)***		***(n=29)***		
mean HU	-745.84	62.84	-710.31	67.9	-760.83	54.5	0.0003 t-test	-710.31	67.9	-767.37	53.62	-752.95	55.43	0.001 ANOVA
RUL*	***(n=91)***		***(n=27)***		***(n=64)***			***(n=27)***		***(n=35)***		***(n=29)***		
mean HU	-753.56	64.74	-725.07	71.2	-765.58	58.31	0.0057 t-test	-725.07	71.2	-774.61	55.99	-754.68	60.15	0.01 ANOVA
RML *	***(n=91)***		***(n=27)***		***(n=64)***			***(n=27)***		***(n=35)***		***(n=29)***		
mean HU	-784.4	56.93	-753.53	64.9	-797.42	48.07	0.0006 t-test	-753.53	64.9	-800.22	51.45	-794.05	44.3	0.0025 ANOVA
RLL *	***(n=91)***		***(n=27)***		***(n=64)***			***(n=27)***		***(n=35)***		***(n=29)***		
mean HU	-714.78	78.31	-669.49	73.76	-733.89	72.56	0.0002 t-test	-669.49	73.76	-738.74	74.85	-728.04	69.24	0.001 ANOVA

 # - nonparametric variables
**** -parametric variables***

9.3.5. Emphysema score

Emphysema scores are the percentage of the whole lung volume at full inspiration with a lung density of –950 HU or lower [see page 52].

There was no observed difference in the emphysema score for both lungs (combined) between subjects with and without PPTB (t-test p=0.1952). Similarly, no difference was found between the left lung alone, right lung alone, LUL, LLL, RUL and RML [see **Table 75**]. However, the RLL showed numerically more emphysema in subjects with PPTB compared to those without (25.6% vs. 21.4%), but this was of borderline statistical significance (Wilcoxon p=0.055). On three-group analysis, subjects with DPTB had higher emphysema scores than those with PrPTB and NPTB, for the whole left lung (p=0.032), the right lung (p=0.044), LUL (p=0.018) and RUL (p=0.034). A similar trend was observed for both lungs combined (p=0.062), the RML (p=0.098) and RLL (p=0.059). There was no difference in emphysema scores between the three subgroups only in the LLL (p=0.11) [see **Table 75**].

9.3.6. Gas trapping score

Gas trapping scores are the percentage of the whole lung volume at full expiration (RV) with a lung density of –860 or less [see page 72].

Gas trapping scores were significantly higher for both lungs combined (36.0% vs. 26.7%, t-test p=0.0062) in subjects with PPTB than in those without, and in comparisons of the three subgroups: DPTB 38.9%, PrPTB 32.8% and NPTB 26.7% (ANOVA p=0.0061) [see Table 76]. Subjects with PPTB had significantly higher gas trapping scores for both the left and right lungs alone (p=0.016 and p=0.0019), the LUL (p=0.006), RUL (p=0.0047), RML (p=0.0041) and RLL (p=0.001). This finding was also highly significant in the analysis of the three subgroups, with intermediate values for the PrPTB group [see Table 76]. Only in the LLL was the gas trapping score not statistically different in those with PPTB.

Table 75: Comparison of emphysema scores (using –950 HU cut-point), according to PPTB status.

	All	sd	NPTB	sd	PPTB	sd	*p-value*	*test*	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
(n)	(94)		(28)		(66)				(28)		(35)		(31)			
Total*																
mean	25.8	8.78	23.99	7.14	26.57	9.33	*0.1952*	*t-test*	23.99	7.14	28.56	8.1	24.32	10.22	*0.062*	*ANOVA*
Left Lung*																
mean	25.78	9.03	24.21	7.45	26.44	9.6	*0.2767*	*t-test*	24.21#	7.45	28.4#	8.33	24.23#	10.56	*0.0318*	*Kwallis*
median	26.1		23.41		26.29				23.41		28		21.5			
LUL*																
mean	27.32	9.49	25.64	7.69	28.03	10.13	*0.2679*	*t-test*	25.64#	7.69	30.45#	9.12	25.29#	10.66	*0.0179*	*Kwallis*
median	27.05		25.09		28.7				25.09		29.9		23.69			
LLL#																
mean	23.67	9.58	22	8.43	24.38	10.01	*0.3171*	*Wilcoxon*	*22#*	8.43	25.83#	8.93	22.75#	11.02	*0.1101*	*Kwallis*
median	22.36		22.18		22.83				22.18		25.72		19.92			
Right Lung*																
mean	25.86	8.94	23.77	6.97	26.75	9.56	*0.1395*	*t-test*	23.77	6.97	28.81	8.77	24.42	10.02	*0.0441*	*ANOVA*
RUL*																
mean	26.9	9.24	25.32	7.78	27.58	9.78	*0.2809*	*t-test*	25.32	7.78	30.09	9.53	24.74	9.4	*0.0335*	*ANOVA*
RML*																
mean	27.22	9.69	24.86	7.62	28.22	10.34	*0.1246*	*t-test*	24.86	7.62	29.91	10.46	26.32	10.02	*0.098*	*ANOVA*
RLL*																
mean	24.23	10.43	21.12	7.29	25.55	11.3	*0.0599*	*t-test*	21.12	7.29	27.28	10.43	23.58	12.08	*0.0594*	*ANOVA*
median	23.4		21.42		24.78		*0.0551*	*Wilcoxon non equal variances*	21.42		26.98		20.94			

(values indicate the % of lung parenychyma below -950HU)
 # - nonparametric variables
** -parametric variables*

Table 76: Comparison of gas trapping scores (using –860 HU cut-point), according to PPTB status.

	All	sd	NPTB	sd	PPTB	sd	*p-value*	*test*	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
(n)	**(94)**		**(28)**		**(66)**				**(28)**		**(35)**		**(31)**			
Total*																
mean	33.24	15.31	26.69	13.02	36.02	15.44	*0.0062*	*t-test*	26.69	13.02	38.86	15.05	32.82	15.49	*0.0061*	*ANOVA*
Left Lung#																
mean	31.99	16.1	25.8	13.03	34.61	16.63	*0.0158*	*Wilcoxon*	25.8	13.03	37.31	16.88	31.57	16.08	*0.025*	*Kwallis*
median	27.27		22.5		30.73				22.5		35.07		28.77			
LUL*																
mean	35.63	16.86	28.38	13.81	38.71	17.19	*0.006*	*t-test*	28.38	13.81	41.72	17.39	35.3	16.57	*0.0065*	*ANOVA*
LLL#	***(n=93)***		***(n=27)***		***(n=66)***				***(n=27)***		***(n=35)***		***(n=31)***			
mean	26.98	16.95	22.23	13.84	28.92	17.8	*0.1194*	*Wilcoxon*	22.23	13.84	31.2	18.75	26.35	16.58	*0.205*	*Kwallis*
median	21.71		19.64		22.24				19.64		25.76		21.75			
Right Lung*	***(n=91)***		***(n=27)***		***(n=64)***				(n=27)		(n=35)		(n=29)			
mean	34.65	15.25	27.16	13.37	37.81	14.97	*0.0019*	*t-test*	27.16	13.37	40.29	14.81	34.82	14.87	*0.0027*	*ANOVA*
RUL*	***(n=91)***		***(n=27)***		***(n=64)***				(n=27)		(n=35)		(n=29)			
mean	36.61	16.36	29.26	14.64	39.71	16.15	*0.0047*	*t-test*	29.26	14.64	42.77	16.73	36.03	14.87	*0.0044*	*ANOVA*
RML*	***(n=91)***		***(n=27)***		***(n=64)***				(n=27)		(n=35)		(n=29)			
mean	42.25	16.28	34.81	15.57	45.38	15.65	*0.0041*	*t-test*	34.81	15.57	46.76	16.43	43.72	14.76	*0.0123*	*ANOVA*
RLL#	***(n=91)***		***(n=27)***		***(n=64)***				(n=27)		(n=35)		(n=29)			
mean	28.63	17.23	20.28	13.03	32.15	17.65	*0.001*	*Wilcoxon*	20.28	13.03	34.33	17.77	29.52	17.46	*0.0022*	*Kwallis*
median	24.11		18.47		27.84				18.47		28.55		24.73			

(values indicate the % of lung parenychyma below -860HU)
 # - nonparametric variables
** -parametric variables*

9.3.7. Corrected gas trapping scores at residual volume

Areas of emphysematous lung have the potential to increase the gas trapping scores in CT scans performed at residual volume. For this reason, gas trapping scores may be corrected for areas of emphysema. This is performed by subtracting a subject's emphysema score (which is measured at TLC) from the gas trapping score (measured on RV). These corrected gas trapping scores are presented in Table 77, and the distribution for the right and left lungs are seen in Figure 55 and Figure 56, respectively.

Subjects with PPTB had significantly higher corrected gas trapping scores than those with NPTB (median 9.5% vs. 2.7%, Wilcoxon p=0.0036). Moreover, subjects with DPTB had significantly higher corrected gas trapping scores (median 10.3%), compared with subjects with PrPTB (median 8.5%) or NPTB (median 2.7%) (Kruskal-Wallis p=0.011) [see Table 77}.

Similarly, both right and left lungs individually, as well as all-individual lobes (except the LLL) demonstrated significantly greater corrected gas trapping scores in subjects with PPTB, compared to those without. On three-group analysis, higher corrected gas trapping scores were observed in subjects with DPTB compared with NPTB, for both lungs and all lobes (except the LLL), while subjects with PrPTB had intermediary values [see Table 77].

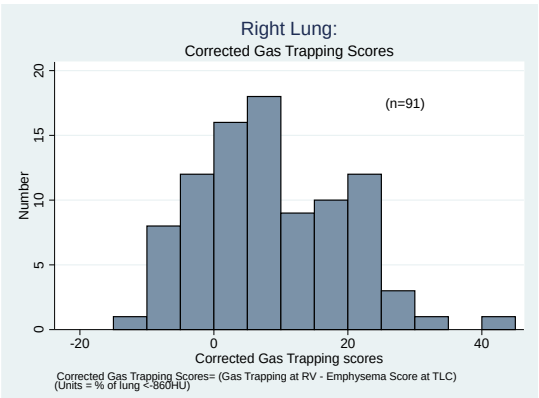


Figure 55: Distribution of corrected gas trapping scores - right lung.

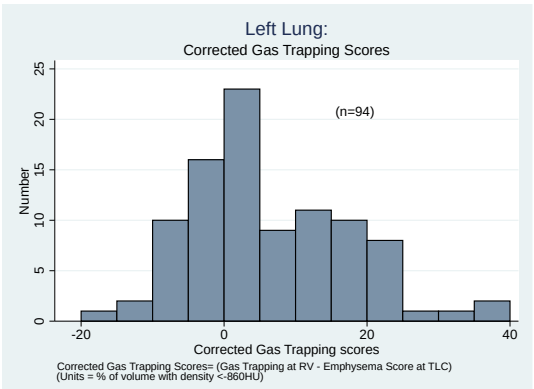


Figure 56: Distribution of corrected gas trapping scores - left lung.

9.3.8. Fibrosis scores

Fibrosis was defined as percentage area of lung parenchyma with density scores of –200 HU or greater on CT scans performed at full inspiration.

There was no significant difference in the fibrosis scores between those with and without PPTB (2.3% vs. 2.1%, respectively, Wilcoxon p=0.370). In subjects with PPTB, only the RUL showed a significantly greater fibrosis score than in those with NPTB (Wilcoxon p=0.0336), and no difference was observed between these groups for the right and left lung overall, or in other individual lobes [see Table 78].

However, on analysis of the three groups, subjects with DPTB showed significantly greater fibrosis scores for both lungs combined (p=0.0547), for the right lung (0.0175) and RUL (0.0014) compared with those with PrPTB and NPTB, while the LUL and RLL also demonstrated a trend toward higher fibrosis scores [see Table 78].

Table 77: Comparison of corrected gas trapping scores[§], according to PPTB status.

	All	sd	NPTB	sd	PPTB	sd	*p-value*	*test*	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
(n)	(94)		(28)		(66)				(28)		(35)		(31)			
Total#																
mean	7.44	10.7	2.69	8.69	9.45	10.89	*0.0036*	*Wilcoxon*	2.69	8.69	10.3	11.7	8.49	10	*0.0105*	*Kwallis*
median	5.73		1.71		7.6				1.71		9.08		6.14			
Left Lung*																
mean	6.21	11.35	1.59	9.27	8.17	11.64	*0.0094*	*t-test*	1.59	9.27	8.92	13.06	7.34	9.95	*0.0294*	*ANOVA*
LUL*																
mean	8.31	12.33	2.73	9.99	10.68	12.53	*0.0038*	*t-test*	2.73#	9.99	11.27#	13.65	10.01#	11.32	*0.0112*	*Kwallis*
median	7.52		0.88		9.16				0.88		10.7		6.59			
LLL#																
mean	3.23	11.73	0.029	9.01	4.54	12.5	*0.1116*	*Wilcoxon*	0.029	9.01	5.37	14.48	3.6	9.97	*0.2799*	*Kwallis*
median	0.9		-3.18		3.21				-3.18		5.12		3.06			
Right Lung*	***(n=91)***		***(n=27)***		***(n=64)***				***(n=27)***		***(n=35)***		***(n=29)***			
Mean	8.5	10.64	3.23	8.84	10.72	10.61	*0.018*	*t-test*	3.23	8.84	11.48	10.93	9.81	10.34	*0.0063*	*ANOVA*
RUL*	***(n=91)***		***(n=27)***		***(n=64)***				***(n=27)***		***(n=35)***		***(n=29)***			
Mean	9.42	11.66	3.79	9.44	11.8	11.75	*0.0023*	*t-test*	3.79	9.44	12.68	11.86	10.74	11.73	*0.0078*	*ANOVA*
RML*	***(n=91)***		***(n=27)***		***(n=64)***				***(n=27)***		***(n=35)***		***(n=29)***			
mean	14.78	11.97	9.73	10.89	16.91	11.84	*0.0082*	*t-test*	9.73	10.89	16.85	12.47	16.97	11.24	*0.031*	*ANOVA*
RLL#	***(n=91)***		***(n=27)***		***(n=64)***				***(n=27)***		***(n=35)***		***(n=29)***			
mean	4.08	11.47	-0.99	9.04	6.22	11.76	*0.0022*	*Wilcoxon*	-0.99	9.04	7.04	12.68	5.23	10.69	*0.0086*	*Kwallis*
median	1.94		-2.11		3.38				-2.11		3.68		3.28			

§- Corrected gas trapping score = (860 HU score at RV – 950HU score at TLC)
(values indicate the adjusted % of lung parenchyma below threshold)
 # - nonparametric variables
** -parametric variables*

Table 78: Comparison of fibrosis scores (using –200 HU cut-point), according to PPTB status.

	All	sd	NPTB	sd	Prev TB	sd	*p-value*	*test*	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
(n)	(94)		(28)		(66)				(28)		(35)		(31)			
Total#																
mean	2.25	0.59	2.13	0.45	2.3	0.64	*0.3697*	*Wilcoxon*	2.13	0.45	2.44	0.63	2.15	0.62	*0.0547*	*Kwallis*
median	2.14		2.08		2.15				2.08		2.28		2.11			
Left Lung#																
mean	2.22	0.71	2.1	0.49	2.26	0.78	*0.6434*	*Wilcoxon*	2.1	0.49	2.35	0.71	2.17	0.86	*0.254*	*Kwallis*
median	2.09		2.03		2.11				2.03		2.2		2.09			
LUL#																
mean	2.2	1.08	1.95	0.46	2.31	1.24	*0.3853*	*Wilcoxon*	1.95	0.46	2.49	1.09	2.11	1.39	*0.0616*	*Kwallis*
median	1.97		1.88		2.01				1.88		2.31		1.94			
LLL#																
mean	2.29	0.73	2.29	0.57	2.29	0.79	*0.4568*	*Wilcoxon*	2.29	0.57	2.3	0.72	2.27	0.87	*0.6999*	*Kwallis*
median	2.21		2.29		2.18				2.29		2.17		2.18			
Right Lung#																
mean	2.3	0.63	2.16	0.44	2.36	0.69	*0.4568*	*Wilcoxon*	2.16	0.44	2.54	0.7	2.16	0.63	*0.0175*	*Kwallis*
median	2.17		2.18		2.16				2.18		2.33		2.05			
RUL#																
mean	2.44	1.23	1.97	0.47	2.63	1.39	*0.0336*	*Wilcoxon*	1.97	0.47	2.86	1.19	2.38	1.56	*0.0014*	*Kwallis*
median	2.09		1.91		2.18				1.91		2.4		1.9			
RML#																
mean	1.89	0.7	1.94	0.56	1.87	0.76	*0.2149*	*Wilcoxon*	1.94	0.56	1.98	0.92	1.74	0.5	*0.2322*	*Kwallis*
median	1.85		2.03		1.8				2.03		1.88		1.63			
RLL#																
mean	2.47	0.82	2.45	0.52	2.46	0.93	*0.5517*	*Wilcoxon*	2.45	0.52	2.68	1.12	2.22	0.56	*0.0988*	*Kwallis*
median	2.31		2.4		2.28				2.4		2.3		2.1			

(values indicate the % of lung parenychyma above -200HU)
 # - nonparametric variables

9.3.9. Correlation between gas trapping and fibrosis scores

An analysis of the correlation between the fibrosis scores (–200 HU or higher on TLC scans) and gas trapping (–860 HU or lower on RV scans) was performed. Spearman's rank correlation coefficient (rho) was used to estimate level of correlation, and the coefficient of determination (R^2) was calculated using simple linear regression.

A significant correlation was found between the gas trapping and the fibrosis scores for all subjects when combined (Spearman's correlation coefficient); both lungs combined (rho=0.256, p=0.0128), left and right lungs alone, LUL, LLL and RLL. However the coefficients of determination (R^2) were small for most of the comparisons, ranging from 0.0026 to 0.068 [see Table 79].

This relationship between gas trapping and fibrosis scores was present for subjects in the NPTB and PrPTB groups, but not the DPTB group - the correlation coefficients and coefficients of determination (R^2) being greater for subjects in the former group. The R2 values ranged from 0.117 to 0.300 for the NPTB group, and from 0.0121 to 0.289 for the PrPTB group [see **Table 80**].

In contrast, there was no significant relationship between gas trapping and fibrosis scores for the DPTB group (rho for both lungs 0.1905, p=0.273), and R^2 values ranged from –0.0179 to 0.0784. Spearman correlation coefficients were approximately zero for the right lung, RUL, and LUL, implying no association [see **Table 80** and Figure 57].

Thus, the association between gas trapping and fibrosis scores was limited to the group with NPTB, but the group with PrPTB demonstrated intermediate levels of correlation.

Table 79: Correlation of gas trapping scores with fibrosis scores, according to PPTB status: NPTB vs. PPTB.

	All	p-value	NPTB	p-value	PPTB	p-value
Total	(n=94)		(n=28)		(n=66)	
Spearman's Coefficient	0.2558	0.0128	0.5479	0.0025	0.2061	0.0969
R-squared	0.048	0.0339	0.2383	0.0084	0.0467	0.0813
Left Lung	(n=94)		(n=28)		(n=66)	
Spearman's Coefficient	0.3375	0.0009	0.5047	0.0062	0.3004	0.0143
R-squared	0.0657	0.0127	0.1984	0.0175	0.0698	0.0321
LUL	(n=94)		(n=28)		(n=66)	
Spearman's Coefficient	0.2115	0.0407	0.5528	0.0023	0.1476	0.2369
R-squared	0.035	0.0711	0.271	0.0045	0.0471	0.0799
LLL	(n=93)		(n=27)		(n=66)	
Spearman's Coefficient	0.3333	0.0011	0.3187	0.1052	0.325	0.0077
R-squared	0.0551	0.0235	0.1911	0.0226	0.0415	0.101
Right Lung	(n=91)		(n=27)		(n=64)	
Spearman's Coefficient	0.207	0.049	0.5598	0.0024	0.145	0.2531
R-squared	0.0125	0.2915	0.2452	0.0086	0.0112	0.4048
RUL	(n=91)		(n=27)		(n=64)	
Spearman's Coefficient	0.1189	0.2617	0.5446	0.0033	0.0587	0.6447
R-squared	0.0026	0.6292	0.3	0.0031	0.0013	0.7738
RLL	(n=91)		(n=27)		(n=64)	
Spearman's Coefficient	0.32	0.002	0.254	0.2011	0.339	0.0061
R-squared	0.0677	0.0128	0.1173	0.0803	0.0743	0.0293

Table 80: Correlation of gas trapping scores with fibrosis scores, according to PPTB status: three-group analysis.

	NPTB	p-value	DPTB	p-value	PrPTB	p-value
Total	(n=28)		(n=35)		(n=31)	
Spearman's Coefficient	0.5479	0.0025	0.1905	0.2731	0.3835	0.0332
R-squared	0.2383	0.0084	0.0359	0.2755	0.1341	0.0427
Left Lung						
Spearman's Coefficient	0.5047	0.0062	0.2336	0.1768	0.4907	0.0051
R-squared	0.1984	0.0175	0.075	0.1115	0.0963	0.0892
LUL						
Spearman's Coefficient	0.5528	0.0023	0.0527	0.7638	0.4583	0.0095
R-squared	0.271	0.0045	0.0277	0.3392	0.1161	0.0607
LLL	(n=27)		(n=35)		(n=31)	
Spearman's Coefficient	0.3187	0.1052	0.2499	0.1477	0.4375	0.0138
R-squared	0.1911	0.0226	0.0784	0.1034	0.0186	0.4639

	NPTB	p-value	DPTB	p-value	PrPTB	p-value
Right Lung	(n=27)		(n=35)		(n=29)	
Spearman's Coefficient	0.5598	0.0024	0.0653	0.7095	0.3635	0.0526
R-squared	0.2452	0.0086	0.0024	0.7787	0.1012	0.0925
RUL						
Spearman's Coefficient	0.5446	0.0033	-0.0179	0.9186	0.2389	0.212
R-squared	0.3	0.0031	0.0125	0.522	0.0121	0.5704
RLL	(n=27)		(n=35)		(n=29)	
Spearman's Coefficient	0.254	0.2011	0.2714	0.1147	0.5448	0.0022
R-squared	0.1173	0.0803	0.0599	0.1564	0.2893	0.0015

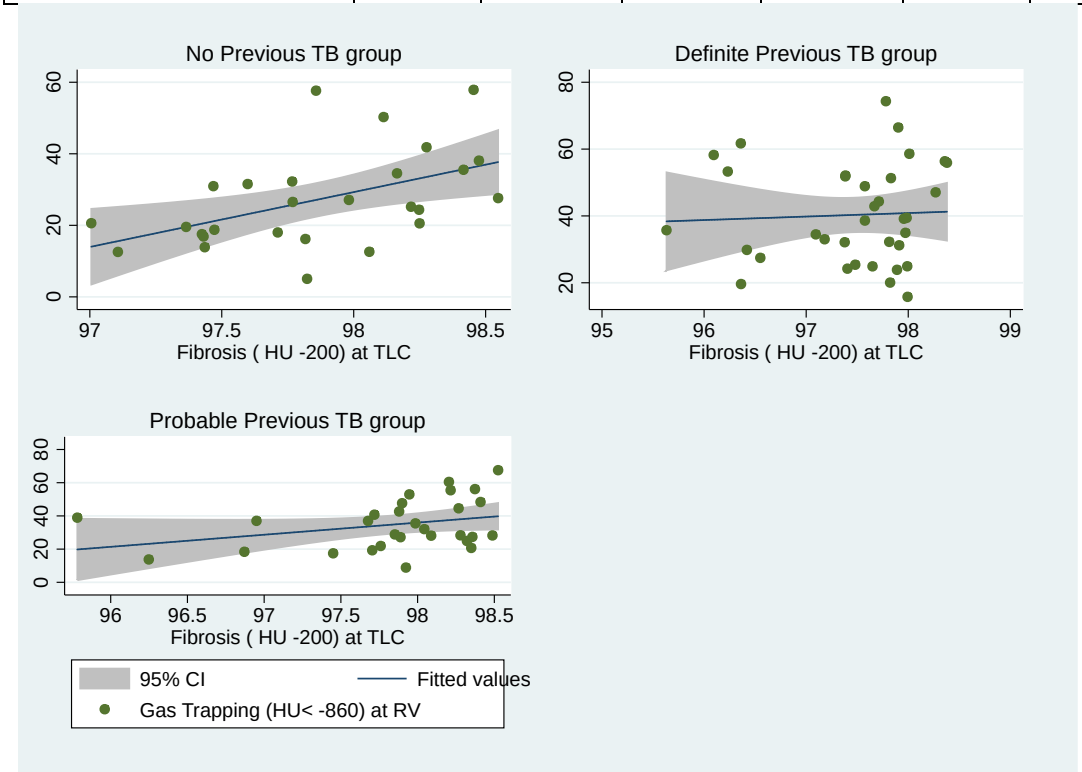


Figure 57: Correlation of fibrosis scores with gas trapping scores, for the right lung.

9.4. Imaging analysis only in subjects with chronic airflow obstruction

In an attempt to limit a type 1 error, an analysis restricted to subjects who were confirmed to have CAO at Visit 2 (i.e. confirmed CAO in the Follow-up study) was performed for the variables described above. On this basis 17 of 94 subjects (18.1%) were excluded: nine (52.9%) from the NPTB group, one (5.9%) from DPTB and seven (41.1%) from the PrPTB group. In one

additional subject, whole body plethysmography was unsuccessful, and of the remainder, two subjects had incomplete CT scan quantification data.

Selected results of this analysis are presented in Appendix 8 - Results of Lung Imaging, only for Subjects with Chronic Airflow Obstruction.

Results of the lung and lobar volume assessment were consistent with the previous analysis of all subjects and showed only reduced percentage volume of the RUL in subjects with PPTB, compared to subjects with NPTB.

Similarly, the analysis of bronchial wall measurements was consistent with that of the full cohort, and the Pi10 was not significantly different between subjects with and without PPTB, nor on three-group analysis [see Appendix 8].

In contrast to the full cohort analysis, after removal of subjects with CAO, the average lung density at TLC (inspiratory scan) was no longer significantly different between subjects with and without PPTB, for either lungs or the lobes. This finding was consistent on three-group analysis. The RLL displayed a trend to less dense lungs ($p=0.0527$) on comparison of NTPB and PPTB, but not on three-group analysis [see Appendix 8].

The findings of re-analysis of the average lung density at residual volume (expiratory scan) were consistent with analysis of the whole cohort, and showed lower mean densities in subjects with PPTB compared to those with NPTB for: both lungs combined, right and left lungs alone, RML, RLL and LUL (trend to significance). Three-way analysis reduced the statistical significance of some of these findings [see Appendix 8]; however, when the DPTB and NPTB groups were compared directly with exclusion of the PrPTB group, the DPTB group showed significantly lower densities for: both lungs combined, right lung, left lung, RML, RLL and LUL (trend to significance).

In contrast to the analysis of the full cohort, when analysing only subjects with CAO, the emphysema scores were not found to be statistically significantly different between those with and without PPTB, for both lung combined, right and left lungs individually, as well as all lobes. This observation was confirmed on three-group analysis [see Appendix 8].

Re-analysis of gas trapping scores in subjects with PPTB showed a trend towards significantly greater scores in those with PPTB compared to those with NPTB, for both lungs combined. However, there were significantly greater scores for the right lung alone, RML and RLL in subjects with PPTB, as well as a trend towards greater scores for the LUL. Three-way analysis demonstrated significant differences in only the RLL gas trapping scores. However, on direct comparison of the DPTB and NPTB groups, with exclusion of PrPTB group, significantly higher gas trapping scores were observed for subjects with DPTB in: both lungs combined, the right lung, RUL, RLL and LUL, while the left lung and RML demonstrated a trend to significance [see Appendix 8].

The corrected gas trapping score for both lungs was higher in subjects with PPTB than those with NPTB, however did not attain statistical significance (p=0.0583). The values for the right lung alone and the RLL were significantly higher in those with PPTB, while a trend to higher values was also seen in the left lung alone, the LUL, RUL and RML. Three-group analysis was unable to confirm these findings, but direct comparison of subjects in the DPTB and NPTB groups, showed significantly higher values in the DPTB in keeping with the above [see Appendix 8]. The analysis of the fibrosis scores only in subjects with CAO yielded results entirely consistent with the analysis of the full cohort [see Appendix 8].

9.4.1. Comparison of subjects with and without CAO in the NPTB group (sensitivity analysis)

In the above analysis, 17 subjects without CAO were excluded, nine of whom were from the NPTB group, and one from the DPTB group. Thus, a sensitivity analysis was performed to determine if differences within the NPTB group between subjects with and without CAO could account for some of the observed discrepancies with the full cohort analysis [see Table 81].

A trend towards greater emphysema scores in the subjects with NPTB and CAO was found, compared to those without CAO (for both lungs 25.7% vs. 20.4%, t-test p=0.0617). The gas trapping scores were significantly

greater in subjects with CAO compared to those without (for both lungs 30.1% vs. 19.6%, t-test p=0.0437). But, there was no significant difference in the corrected gas trapping scores between subjects with and without CAO (t-test p=0.147) [see Table 81].

Table 81: Comparison of imaging findings between subjects in the NPTB group, with and without CAO.

	NO COPD	**sd**	**COPD**	sd	***p-value***	***test***
(n)	(9)		(19)			
Emphysema (-950HU)						
Total*						
mean	20.35	7.22	25.72	6.6	*0.0617*	*t-test*
median	21.46		28.19			
Left Lung*						
mean	20.48	7.69	25.98	6.83	*0.0668*	*t-test*
median	21.35		28.43			
Right Lung*						
mean	20.21	6.84	25.45	6.53	*0.0614*	*t-test*
median	21.55		26.35			
Gas Trapping (-860HU)	(n=9)		(n=19)			
Total*						
mean	19.55	9.04	30.07	13.43	*0.0437*	*t-test*
median	19.97		27.1			
Left Lung#						
mean	19.06	9.14	29	13.57	*0.0463*	*Wilcoxon*
median	19.35		25			
Right Lung*	(n=9)		(n=18)			
mean	19.96	9.04	30.76	13.91	*0.0455*	*t-test*
median	19.55		27.35			
Corrected Gas Trapping (Gas trapping score – emphysema score)						
Total*	(n=9)		(n=19)			
mean	-0.78	6.86	4.35	9.14	*0.1468*	*t-test*
median	-3.75		4.08			
Left Lung*						
mean	-1.42	7.47	3.01	9.87	*0.2442*	*t-test*
median	-4.46		2.36			
Right Lung#	(n=9)		(n=18)			
mean	-0.25	6.43	4.97	9.5	*0.1358*	*Wilcoxon*
median	-3.22		3.854			

 # - nonparametric variables
** -parametric variables*

9.5. Summary of findings

The quantitative assessment of the CT lung images provided the following results:

The volume of the RUL but not the LUL was reduced in subjects with PPTB and especially with DPTB in both the full cohort, and only subjects with CAO. This result is a useful sensitivity indicator as the RUL is the most frequent and severely involved lobe in PTB.

A slightly higher emphysema score found in subjects with PPTB was not confirmed when subjects without CAO were excluded. In contrast, gas trapping (measured at full expiration) was greater in both lungs and in the majority of lobes in subjects with PPTB, even when corrected by excluding areas with emphysema detected at TLC (the corrected gas trapping score). These results were similar when subjects without CAO were excluded although reduced numbers reduced the statistical significance of the observation.

Apart from the RUL, fibrosis scores in the remaining lobes were not significantly different between subjects with and without PPTB. Although increased fibrosis scores were found in analysis of the whole right lung and in both lungs combined, these were presumed to reflect RUL fibrosis.

No association was demonstrated between fibrosis scores and gas trapping scores in DPTB, but a significant correlation was seen in subjects with NPTB, the reason for which is not apparent.

Finally, the thickness of the airway walls, measured as the Pi10, was similar in subjects with and without PPTB.

Chapter 10. Results of the Multivariate Analysis of the Relationship between Demographic and Clinical Features, Lung Physiology and Structural Abnormalities in Subjects with COPD and TOPD

10.1. Introduction

The relationship between structural changes observed on CT imaging and abnormalities in lung physiology were examined by multivariate analysis. A particular focus was to explore differences between subjects with and without previous pulmonary TB (PPTB). The dependent variables analysed were: diffusing capacity (DL_{CO} - expressed as percentage of predicted value) and inspiratory capacity (IC - percentage of predicted), and CT scores for emphysema, corrected gas trapping and fibrosis. These were examined for both lungs (combined) and, for simplicity, only the right lung, right upper and lower lobes were included as part of this analysis.

The independent variables used in the multivariate analysis were [see Table 82]:

- Age
- Gender
- Cigarette usage (pack-years)
- Cannabis usage (joint-years)
- Asthma status, defined previously [see page 116]
- Previous Tuberculosis status, [presented on page 141] as
    - No previous TB (NPTB)
    - Probable Previous TB (PrPTB)
    - Definite Previous TB (DPTB)

Table 82: Summary of independent variables.

Age	*(n=107)*	
	Mean=63.01yrs	sd=9.719
Gender	*(n=107)*	
Male	49	(45.8%)
Female	58	(54.2%)
Cigarette (pack-years)	*(n=105)*	
	Mean=23.413	sd=22.351
	Median=18.7	
Cannabis (joint-years)	*(n=105)*	
	Mean=44.813	sd=187.84
Asthma status	*(n=106)*	
No asthma	88	
Asthma	18	
Previous TB status	*(n=104)*	
No previous TB (NPTB)	31	
Probable Previous TB (PrPTB)	34	
Definite Previous TB (DPTB)	39	
(withdrew)	(3)	

The right upper and right lower lobes were selected because relationships on univariate analysis between structural changes and physiology in these lobes were more consistent than those from the upper and lower lobes of the left lung.

For all dependent variables, two methods of multivariate analysis were performed. A full model with all independent variables included, as well as backward stepwise regression, where variables were removed from the model if their significance was $p>0.10$, and were allowed to re-enter the model if their significance became $p<0.08$. Additionally, as a sensitivity measure, regression modelling was performed for all dependent variables using simple backward regression**,** simple forward regression and then stepwise forward regression. The results obtained from these analyses were not materially different, and consequently they are not presented here.

10.2. Multivariate analysis for diffusing capacity (percentage of predicted)

[See Table 83 and **Table 84**]

10.2.1. Full model

Table 83: Multivariate analysis for diffusing capacity using a full model.

			Coef	SE	t	P>|t|	95% CI	
Number of Obs	102	**Age**	0.142	0.217	0.650	0.516	-0.290	0.573
F	3.21	**Gender**	-2.777	4.418	-0.630	0.531	-11.548	5.995
Prob > F	0.0043	**Cig Pack Yr**	-0.175	0.106	-1.660	0.101	-0.386	0.035
R-squared	0.1927	**Can Joint Yr**	0.024	0.012	1.960	0.053	0.000	0.049
Adj R-sq	0.1326	**Asthma**	10.794	5.728	1.880	0.063	-0.579	22.167
Root MSE	20.405	**PrPTB**	-10.859	5.178	-2.100	0.039	-21.141	-0.578
		DPTB	-17.740	5.120	-3.460	0.001	-27.906	-7.574
		Constant	73.202	14.462	5.060	0.000	44.487	101.917

10.2.2. Backward stepwise regression

Table 84: Multivariate analysis for diffusing capacity using backward stepwise regression.

Number of Obs	102		**Coef**	**SE**	**t**	**P>|t|**	**95% CI**	
F	5.71	**PrPTB**	-10.362	5.185	-2.000	0.048	-20.651	-0.074
Prob > F	0.0012	**DPTB**	-16.279	5.035	-3.230	0.002	-26.272	-6.286
R-squared	0.1487	**Asthma**	11.493	5.511	2.090	0.040	0.556	22.430
Adj R-sq	0.1227	**Constant**	76.818	3.961	19.390	0.000	68.957	84.679
Root MSE	20.522							

.

DL_{CO} (% predicted) was significantly lower in subjects with DPTB and PrPTB, compared with NPTB. In subjects with DPTB, the mean DL_{CO} was 16.3% lower (p=0.002), and in subjects with PrPTB it was 10.4% lower (p=0.048) than in those with NPTB.

Using the full model, cannabis use and the presence of asthma was associated with a trend towards a higher DL_{CO} [see Table 83]. However, on backward stepwise regression, a significant association persisted only in asthma, with an 11.5% increase in DL_{CO} (p=0.04).

When asthma was removed from the regression modeling, both cigarette smoking and cannabis smoking showed significant associations with DL_{CO} [see Table 85]. The likely explanation is confounding between 'smoking' and 'asthma', as a minimal or negative smoking history was a criterion used in the diagnosis of subjects as having asthma.

Table 85: Multivariate analysis for diffusing capacity using backward stepwise regression, with asthma not included in the model.

	Coeff	SE	T	P>|t|	95% CI	
Probable TB	-10.975	5.108	-2.15	0.034	-21.112	-0.839
Definite TB	-18.688	4.987	-3.75	0.000	-28.584	-8.791
Cig Pack Yr	-0.203	0.101	-2.01	0.047	-0.403	-0.003
Can Joint Yr	0.0245	0.0121	2.02	0.046	0.005	0.049
Constant	83.535	4.201	19.88	0.000	75.198	91.872

10.3. Multivariate analysis for inspiratory capacity (percentage of predicted)

Data on 99 subjects were included in this analysis, as four subjects in the cohort of 104 subjects were unable to perform reproducible manoeuvres and one subject was older than 80 years. Asthma status could not be imputed in one subject (owing to missing information). The models are show in Table 86 and Table 88.

10.3.1. Full model

Table 86: Multivariate analysis for inspiratory capacity using a full model.

			Coef	SE	t	P>|t|	95% CI	
		Age	0.721	0.264	2.730	0.008	0.196	1.246
Number of Obs	98	**Gender**	16.862	5.197	3.240	0.002	6.538	27.187
F	6.74	**Cig Pack Yr**	-0.036	0.124	-0.290	0.774	-0.282	0.210
Prob > F	0	**Can Joint Yr**	0.003	0.014	0.230	0.815	-0.025	0.032
R-squared	0.3438	**Asthma**	8.739	6.707	1.300	0.196	-4.585	22.063
Adj R-sq	0.2927	**PrPTB**	-20.748	6.099	-3.400	0.001	-32.866	-8.631
Root MSE	23.437	**DPTB**	-21.528	5.990	-3.590	0.001	-33.428	-9.628
		Constant	63.209	17.191	3.680	0.000	29.057	97.361

10.3.2. Backward stepwise regression

Table 87: Multivariate analysis for inspiratory capacity using, backward stepwise regression.

Number of Obs	98		Coef	SE	t	P>|t|	95% CI	
F	11.42	Age	0.673	0.258	2.610	0.010	0.161	1.185
Prob > F	0	Gender	18.339	4.831	3.800	0.000	8.746	27.931
R-squared	0.3294	Probable TB	-20.873	6.056	-3.450	0.001	-32.899	-8.847
Adj R-sq	0.3005	Definite TB	-22.201	5.876	-3.780	0.000	-33.870	-10.532
Root MSE	23.307	Constant	66.460	16.549	4.020	0.000	33.597	99.323

In both the full and backward stepwise regression models: age, gender and PPTB status were associated with IC (% predicted). On backward stepwise regression analysis, subjects with PPTB had an IC 20.9% lower (95% CI –32.9- –8.8%, p=0.001), and subjects with DPTB an IC 22.2% lower (95% CI –33.9%- –10.5%, p<0.001) than subjects with NPTB. In this model, for every 10 years of age, the IC was 6.7% higher (p=0.008). Females had an 18.3% higher IC compared to males (p<0.001).

10.4. Multivariate analysis for CT emphysema score

Ninety-three of 94 subjects with quantitative CT scan data were included in analysis. In one subject asthma status could not be imputed.

10.4.1. Analysis of both lungs combined

Multivariate analysis results for the emphysema score of both lungs combined are presented in Table 88 and Table 90.

10.4.1.1. Full model

Table 88: Multivariate analysis of emphysema score for both lungs, using a full model.

	Coef	SE	t	P>|t|	95% CI	
Age	0.022	0.091	0.240	0.807	-0.159	0.203
Gender	-7.822	1.769	-4.420	0.000	-11.338	-4.305
Cig Pack Yr	-0.010	0.043	-0.230	0.820	-0.095	0.076
Can Joint Yr	0.001	0.005	0.290	0.769	-0.008	0.011
Asthma	0.511	2.291	0.220	0.824	-4.044	5.067
PrPTB	-0.073	2.106	-0.030	0.973	-4.260	4.115
DPTB	3.483	2.079	1.680	0.098	-0.651	7.617
Constant	27.341	5.934	4.610	0.000	15.544	39.139

10.4.1.2. Backward stepwise regression

Table 89: Multivariate analysis of emphysema score for both lungs, using backward stepwise regression.

	Coef	SE	t	P>|t|	95% CI	
DPTB	3.515	1.665	2.110	0.038	0.207	6.823
Gender	-7.710	1.616	-4.770	0.000	-10.920	-4.500
Constant	28.565	1.370	20.850	0.000	25.844	31.286

In both full and backward stepwise regression analyses, female gender was negatively associated with CT emphysema score. Female subjects had a 7.7% lower score than males ($p<0.001$). On backward stepwise regression analysis, DPTB was positively associated with emphysema score; DPTB subjects had a 3.5% higher score than subjects with NPTB ($p=0.038$).

10.4.2. Analysis of right lung

Multivariate analysis results for the emphysema score of the right lung alone are presented in Table 90 and Table 91.

As in the analysis of both lungs with the full model, gender was negatively associated with emphysema score, and subjects in the DPTB group showed a trend towards a positive association. However, using backward stepwise regression, the association with DPTB was positive: a 3.8% higher emphysema score compared with subjects with NPTB

(p=0.026). Female subjects demonstrated a 7.5% lower emphysema score compared to males (p<0.001).

10.4.2.1. Full model

Table 90: Multivariate analysis of emphysema score for right lung, using a full model.

	Coef	SE	t	P>|t|	95% CI	
Age	0.052	0.093	0.560	0.575	-0.132	0.237
Gender	-7.672	1.804	-4.250	0.000	-11.258	-4.086
Cig Pack Yr	-0.021	0.044	-0.470	0.638	-0.108	0.067
Can Joint Yr	0.004	0.005	0.710	0.481	-0.006	0.014
Asthma	0.696	2.337	0.300	0.766	-3.950	5.342
PrPTB	0.186	2.148	0.090	0.931	-4.085	4.456
DPTB	3.914	2.120	1.850	0.068	-0.302	8.129
Constant	25.325	6.051	4.190	0.000	13.294	37.356

10.4.2.2. Backward stepwise regression

Table 91: Multivariate analysis of emphysema score for right lung, using backward stepwise regression.

	Coef	SE	t	P>|t|	95% CI	
DPTB	3.847	1.705	2.26	0.026	0.461	7.234
Gender	-7.538	1.654	-4.56	0.000	-10.824	-4.252
Constant	28.413	1.402	20.26	0	25.628	31.199

10.4.3. Analysis of right upper lobe

Multivariate analysis results for the emphysema score of the right upper lobe alone are presented in **Table 92** and Table 93.

10.4.3.1. Full model

Table 92: Multivariate analysis of emphysema score for right upper lobe, using a full model.

	Coef	SE	t	P>|t|	95% CI	
Age	0.046	0.098	0.470	0.641	-0.148	0.240
Gender	-7.012	1.895	-3.700	0.000	-10.780	-3.245
Cig Pack Yr	0.014	0.046	0.310	0.759	-0.078	0.106
Can Joint Yr	0.001	0.005	0.280	0.782	-0.009	0.012
Asthma	0.820	2.455	0.330	0.739	-4.061	5.701
PrPTB	-1.146	2.257	-0.510	0.613	-5.632	3.341
DPTB	3.670	2.228	1.650	0.103	-0.759	8.099
Constant	26.239	6.358	4.130	0.000	13.598	38.880

10.4.3.2. Backward stepwise regression

Table 93: Multivariate analysis of emphysema score for right upper lobe, using backward stepwise regression.

	Coef	SE	t	P>|t|	95% CI	
DPTB	4.238	1.790	2.370	0.020	0.682	7.794
Gender	-7.094	1.737	-4.080	0.000	-10.544	-3.643
Constant	29.095	1.472	19.760	0.000	26.170	32.021

A negative association was again shown between female gender and emphysema score in both models, being 7.1% less than males ($p<0.001$). Only on backward stepwise regression was the emphysema score of the RUL shown to be significantly higher (4.2%) in subjects with DPTB, compared to the NPTB group ($p<0.001$).

10.4.4. Analysis of right lower lobe

Multivariate analysis results for the emphysema score of the right lower lobe alone are presented in Table 94 and Table 95.

Multivariate analysis of the emphysema score of the right lower lobe showed similar associations to those of the right lung, an association with gender, and a trend toward association for subject with DPTB. Subjects with DPTB had a 3.9% higher ($p=0.056$), and females had 8.4% lower emphysema scores ($p<0.001$) than NPTB and male gender, respectively.

10.4.4.1. Full model

Table 94: Multivariate analysis of emphysema score for right lower lobe, using a full model.

	Coef	**SE**	**t**	**P>|t|**	**95% CI**	
Age	0.080	0.109	0.730	0.466	-0.137	0.296
Gender	-8.581	2.115	-4.060	0.000	-12.785	-4.377
Cig Pack Yr	-0.061	0.052	-1.180	0.243	-0.163	0.042
Can Joint Yr	0.008	0.006	1.380	0.172	-0.004	0.020
Asthma	0.130	2.740	0.050	0.962	-5.317	5.577
PrPTB	1.968	2.518	0.780	0.437	-3.038	6.975
DPTB	4.740	2.486	1.910	0.060	-0.203	9.682
Constant	22.352	7.094	3.150	0.002	8.246	36.457

10.4.4.2. Backward stepwise regression

Table 95: Multivariate analysis of emphysema score for right lower lobe, using backward stepwise regression.

	Coef	SE	t	P>|t|	95% CI	
DPTB	3.929	2.027	1.940	0.056	-0.097	7.955
Gender	-8.432	1.966	-4.290	0.000	-12.339	-4.526
Constant	27.208	1.667	16.320	0.000	23.896	30.520

10.5. Multivariate analysis of CT corrected gas trapping score

The derivation and significance of the corrected gas trapping score is discussed on page 184.

10.5.1 Analysis of both lungs combined

[See Table 96 and Table 97]

10.5.1.1. Full model

Table 96: Multivariate analysis of corrected gas trapping scores for both lungs, using a full model.

	Coef	SE	t	P>|t|	95% CI	
Age	0.114	0.115	0.990	0.326	-0.115	0.342
Gender	-0.637	2.233	-0.290	0.776	-5.077	3.803
Cig Pack Yr	0.063	0.054	1.160	0.251	-0.045	0.171
Can Joint Yr	0.002	0.006	0.370	0.709	-0.010	0.015
Asthma	-5.941	2.893	-2.050	0.043	-11.693	-0.190
PrPTB	4.777	2.659	1.800	0.076	-0.511	10.064
DPTB	6.194	2.625	2.360	0.021	0.975	11.413
Constant	-3.689	7.492	-0.490	0.624	-18.584	11.206

10.5.1.2. Backward stepwise regression

Table 97: Multivariate analysis of corrected gas trapping scores for both lungs, using backward stepwise regression.

	Coef	SE	t	P>|t|	95% CI	
PrPTB	5.232	2.637	1.980	0.050	-0.008	10.472
DPTB	6.473	2.582	2.510	0.014	1.342	11.604
Asthma	-7.184	2.772	-2.590	0.011	-12.692	-1.676
Constant	4.653	2.023	2.300	0.024	0.632	8.673

There was an association with corrected gas trapping score of lungs (combined) and both asthma status (negative association), and DPTB

(positive association), and a trend toward a positive association with PrPTB was seen in the full model.

However, on backward stepwise regression modeling, both subjects in the DPTB and PrPTB groups had significantly higher corrected gas trapping scores compared to subjects with NPTB (6.5% and 5.2% greater scores, respectively, p=0.014 and p=0.050). Subjects with asthma had a 7.2% lower score (p=0.011).

10.5.2. Analysis of right lung

[See Table 98 and Table 99]

10.5.2.1. Full model

Table 98: Multivariate analysis of corrected gas trapping scores for right lung, using a full model.

	Coef	SE	t	P>|t|	95% CI	
Age	0.096	0.116	0.830	0.408	-0.134	0.327
Gender	-0.647	2.220	-0.290	0.772	-5.064	3.770
Cig Pack Yr	0.062	0.054	1.160	0.248	-0.044	0.169
Can Joint Yr	0.002	0.006	0.320	0.749	-0.010	0.014
Asthma	-6.483	2.865	-2.260	0.026	-12.182	-0.784
PrPTB	5.531	2.689	2.060	0.043	0.182	10.880
DPTB	6.759	2.599	2.600	0.011	1.588	11.929
Constant	-1.912	7.447	-0.260	0.798	-16.726	12.902

10.5.2.2. Backward stepwise regression

Table 99: Multivariate analysis of corrected gas trapping scores for right lung, using backward stepwise regression.

	Coef	SE	t	P>|t|	95% CI	
Asthma	-7.758	2.722	-2.850	0.005	-13.169	-2.347
DPTB	7.013	2.553	2.750	0.007	1.938	12.087
PrPTB	6.061	2.643	2.290	0.024	0.807	11.314
Constant	5.350	2.019	2.650	0.010	1.337	9.363

Analysis of the corrected gas trapping scores for the right lung confirmed an association with asthma (negative) and a significant positive association with both DPTB and PrPTB in both models.

Subjects with DPTB had a 7.0% higher (p=0.007) and subjects with PrPTB a 6.1% higher corrected gas trapping score (p=0.024) than subjects with NPTB. Asthma was associated with a 7.8% lower corrected gas trapping score (p=0.005) compared to those without asthma.

10.5.3. Analysis of right upper lobe

[See **Table 100** and Table 101]

10.5.3.1. Full model

Table 100: Multivariate analysis of corrected gas trapping scores for right upper lobe, using a full model.

	Coef	SE	t	P>|t|	95% CI	
Age	0.119	0.127	0.940	0.352	-0.134	0.371
Gender	-1.760	2.433	-0.720	0.471	-6.599	3.079
Cig Pack Yr	0.080	0.059	1.370	0.176	-0.037	0.197
Can Joint Yr	-0.001	0.007	-0.190	0.847	-0.015	0.012
Asthma	-6.588	3.139	-2.100	0.039	-12.831	-0.344
PrPTB	5.776	2.946	1.960	0.053	-0.085	11.637
DPTB	7.440	2.848	2.610	0.011	1.776	13.105
Constant	-2.413	8.159	-0.300	0.768	-18.644	13.818

10.5.3.2. Backward stepwise regression

Table 101: Multivariate analysis of corrected gas trapping scores for right upper lobe, using backward stepwise regression.

	Coef	SE	t	P>|t|	95% CI	
PrPTB	6.405	2.909	2.200	0.030	0.621	12.189
DPTB	7.568	2.810	2.690	0.009	1.982	13.154
Asthma	-8.312	2.996	-2.770	0.007	-14.269	-2.356
Constant	6.058	2.222	2.730	0.008	1.640	10.476

A significant association was again found between corrected gas trapping scores of the RUL and both PPTB status and asthma. Subjects with DPTB having a 7.6% higher (p=0.009), and PrPTB a 6.4% higher score (p=0.030) than NPTB subjects. Subjects with asthma had an 8.3% lower score (p=0.007) than those without asthma.

10.5.4. Analysis of right lower lobe

[See Table 102 and **Table 103**]

10.5.4.1. Full model

Table 102: Multivariate analysis of corrected gas trapping scores for right lower lobe, using a full model.

	Coef	SE	t	P>|t|	95% CI	
Age	0.024	0.129	0.190	0.850	-0.232	0.281
Gender	1.441	2.474	0.580	0.562	-3.481	6.362
Cig Pack Yr	0.032	0.060	0.540	0.590	-0.087	0.151
Can Joint Yr	0.006	0.007	0.910	0.364	-0.007	0.020
Asthma	-6.517	3.192	-2.040	0.044	-12.866	-0.167
PrPTB	5.451	2.996	1.820	0.072	-0.509	11.412
DPTB	6.463	2.896	2.230	0.028	0.702	12.223
Constant	-2.202	8.297	-0.270	0.791	-18.708	14.304
Age	0.024	0.129	0.190	0.850	-0.232	0.281

10.5.4.2. Backward stepwise regression

Table 103: Multivariate analysis of corrected gas trapping scores for right lower lobe, using backward stepwise regression.

	Coef	SE	t	P>|t|	95% CI	
DPTB	6.835	2.823	2.420	0.018	1.223	12.447
PrPTB	5.664	2.923	1.940	0.056	-0.147	11.475
Asthma	-6.901	3.010	-2.290	0.024	-12.886	-0.916
Constant	0.998	2.233	0.450	0.656	-3.440	5.437

Analysis of the right lower lobe revealed similar results on both models, with the corrected gas trapping score being 6.8% higher in subjects with DPTB (p=0.018) and 5.7% higher in PrPTB (trend p=0.056) compared to NPTB. In subjects with asthma, the score was 6.9% lower than those without asthma (p=0.024).

10.6. Multivariate analysis for CT fibrosis score

The fibrosis score was defined as a value of –200 HU or higher.

10.6.1. Analysis of both lungs combined

[See Table 104 and Table 105]

10.6.1.1. Full model

Table 104: Multivariate analysis of fibrosis scores for both lungs, using a full model.

	Coef	SE	t	P>|t|	95% CI	
Age	0.008	0.006	1.220	0.224	-0.005	0.021
Gender	0.347	0.125	2.770	0.007	0.097	0.596
Cig Pack Yr	0.004	0.003	1.220	0.225	-0.002	0.010
Can Joint Yr	-0.000	0.000	-0.590	0.560	-0.001	-0.000
Asthma	-0.071	0.162	-0.440	0.663	-0.394	0.252
PrPTB	0.016	0.149	0.110	0.914	-0.280	0.313
DPTB	0.357	0.147	2.420	0.017	0.064	0.650
Constant	-98.631	0.420	-234.680	0.000	-97.795	-99.466

10.6.1.2. Backward stepwise regression

Table 105: Multivariate analysis of fibrosis scores for both lungs, using a backward stepwise regression.

	Coef	SE	t	P>|t|	95% CI	
DPTB	0.331	0.121	2.750	0.007	0.092	0.571
Gender	0.321	0.117	2.740	0.007	0.089	0.554
Constant	-98.041	0.099	-988.260	0.000	-98.238	-97.844

The CT fibrosis score was significantly higher in subjects with DPTB but not in PrPTB, compared to subjects with NPTB (0.33% higher score, p=0.007). Females had a 0.32% higher score than males (p=0.007).

10.6.2. Analysis of right lung

[See Table 106 and Table 107]

CT fibrosis scores for the right lung alone were also higher in subjects with DPTB, but not PrPTB, compared with subjects with NPTB (0.41% greater score, p=0.002). Females showed a trend towards higher scores for the right lung alone compared with males (p=0.099).

10.6.2.1. Full model

Table 106: Multivariate analysis of fibrosis scores for right lung, using a full model.

	Coef	SE	t	P>|t|	95% CI	
Age	0.009	0.007	1.300	0.197	-0.005	0.023
Gender	0.250	0.134	1.860	0.067	-0.018	0.517
Cig Pack Yr	0.003	0.003	1.060	0.290	-0.003	0.010
Can Joint Yr	-0.000	0.000	-0.180	0.856	-0.001	0.001
Asthma	-0.128	0.174	-0.730	0.464	-0.474	0.218
PrPTB	-0.014	0.160	-0.080	0.933	-0.332	0.305
DPTB	0.408	0.158	2.580	0.012	0.094	0.722
Constant	-98.599	0.451	-218.800	0.000	-99.495	-97.703

10.6.2.2. Backward Stepwise Regression

Table 107: Multivariate analysis of fibrosis scores for right lung, using backward stepwise regression.

	Coef	SE	t	P>|t|	95% CI	
DPTB	0.408	0.129	3.150	0.002	0.151	0.665
Gender	0.209	0.126	1.670	0.099	-0.040	0.459
Constant	-97.961	0.106	-920.010	0.000	-98.172	-97.749

10.6.3. Analysis of right upper lobe

[See Table 108 and Table 109]

In both methods of analysis for the RUL, only subjects with DPTB demonstrated higher fibrosis scores than those in the NPTB group (0.68% increase, p=0.010).

10.6.3.1. Full model

Table 108: Multivariate analysis of fibrosis scores for right upper lobe, using a full model.

	Coef	SE	t	P>|t|	95% CI	
Age	0.014	0.014	0.980	0.329	-0.014	0.041
Gender	0.043	0.268	0.160	0.874	-0.491	0.576
Cig Pack Yr	-0.002	0.007	-0.360	0.716	-0.015	0.011
Can Joint Yr	0.001	0.001	0.850	0.398	-0.001	0.002
Asthma	-0.361	0.347	-1.040	0.302	-1.052	0.330
PrPTB	0.376	0.319	1.180	0.243	-0.259	1.011
DPTB	0.839	0.315	2.660	0.009	0.212	1.466
Constant	-98.787	0.900	-109.780	0.000	-100.577	-96.998

10.6.3.2. Backward stepwise regression

Table 109: Multivariate analysis of fibrosis scores for right upper lobe, using backward stepwise regression.

	Coef	SE	t	P>|t|	95% CI	
DPTB	0.676	0.256	2.650	0.010	0.168	1.184
Constant	-97.817	0.157	-623.910	0.000	-98.129	-97.506

10.6.4. Analysis of Right Lower Lobe

[See Table 110 and Table 111]

10.6.4.1. Full Model

Table 110: Multivariate analysis of fibrosis scores for right lower lobe, using a full model.

	Coef	SE	t	P>|t|	95% CI	
Age	0.012	0.009	1.380	0.171	-0.005	0.029
Gender	0.353	0.169	2.090	0.040	0.017	0.689
Cig Pack Yr	0.013	0.004	3.080	0.003	0.004	0.021
Can Joint Yr	-0.001	0.000	-2.350	0.021	-0.002	-0.000
Asthma	0.030	0.219	0.140	0.890	-0.405	0.466
PrPTB	-0.249	0.201	-1.240	0.220	-0.648	0.151
DPTB	0.324	0.199	1.630	0.106	-0.071	0.719
Constant	-98.770	0.567	-174.290	0.000	-99.897	-97.643

10.6.4.2. Backward Stepwise Regression

Table 111: Multivariate analysis of fibrosis scores for right lower lobe, using backward stepwise regression.

	Coef	SE	t	P>|t|	95% CI	
DPTB	0.441	0.165	2.660	0.009	0.112	0.770
Can Joint Yr	-0.001	0.000	-2.700	0.008	-0.002	-0.000
Gender	0.379	0.167	2.280	0.025	0.048	0.711
Cig Pack Yr	0.013	0.004	3.260	0.002	0.005	0.021
Constant	-98.157	0.174	-564.120	0.000	-98.502	-97.811

Multivariate analysis of the right lower lobe, using both the full and backward stepwise models, confirmed significant associations of fibrosis scores with gender and smoking of both cigarettes and cannabis. In addition, in the backward stepwise regression analysis definite PPTB was also found to be significantly associated with fibrosis. Subjects with definite PPTB had 0.44% higher fibrosis scores compared with subjects with no PPTB (p=0.009).
Females had a 0.38% higher score than males, and in cigarette smokers an increase of 0.13% for every 10-pack-years smoked was observed (p=0.002). By contrast, cannabis smokers had a 0.01% lower fibrosis score for every 10 'joint-years' smoked (p=0.008).

10.7. Summary of findings

These analyses of subjects with CAO confirm associations of PPTB (DPTB and in some instances PrPTB also) with both physiological and radiological features of COPD, suggesting that CAO associated with PPTB is different from usual COPD in several important respects. PPTB-associated CAO is associated with a lower diffusing capacity for carbon monoxide (DL_{CO}) and inspiratory capacity (IC) and higher CT emphysema, corrected gas trapping and fibrosis scores. The associations of some of these features with gender and asthma serve as sensitivity indicators to the significance of the findings. As expected, asthma was associated with a higher DL_{CO} without an increase in emphysema score. Cigarette smoking was associated with a lower DL_{CO}

and had higher fibrosis scores in the right lower lobe (possibly related to 'dirty' lungs from smoke particulates). However, for all physiological and radiological features assessed, namely DL_{CO}, IC, CT emphysema, gas trapping and fibrosis scores, the strength of association with PPTB was dominant over even cigarette smoking. In addition, the finding of both increased emphysema and gas trapping corrected for emphysema suggest airways disease with gas trapping as an important component of disease. Taken together with the absence in significant differences in other physiological measures between COPD and PPTB-associated CAO (FEV1, TLC and RV/TLC), these differences are not explained by differences in the severity of CAO of subjects with PPTB and suggest different structural changes. This is further explored in the next chapter.

Chapter 11. Discussion

11.1. Introduction

The aim of this research was to interrogate tuberculosis-associated obstructed pulmonary disease (TOPD), with the purpose of defining its physiology and radiology, and to compare it with the usual forms of chronic obstructive pulmonary Disease (COPD). The research question arose from the Burden of Obstructive Lung Disease (BOLD) study performed in Cape Town in 2005, which reported a very high prevalence of COPD, higher than sites in other countries, and a high prevalence of a history of previous tuberculosis among the subjects diagnosed with COPD. Another significant observation was the low number of pack-years among smokers, which is further evidence that factors other than tobacco smoking might be important in the pathogenesis of COPD in that community, the most obvious of which are the long-term effects of previous pulmonary tuberculosis (PPTB).

Although this research centered on the description of TOPD as a potential distinct phenotype of COPD, access to the original BOLD study site permitted the design of a follow-up study of some of the original BOLD cohort to address important additional questions. First, to confirm the diagnosis of COPD in subjects who previously fulfilled the diagnostic criteria for COPD in 2005. In conjunction, it afforded the opportunity to perform a critical appraisal of the BOLD method, and its performance in estimating the burden of COPD in communities in the setting of a high prevalence of TB, including the reliability of the specified spirometer. Second, to examine the natural history of COPD in this community, and determine the role, if any, played by PPTB.

Through a process of repeated home visits and contact tracing, a satisfactory response rate was obtained. A total of 107 (54.6%) of the original 196 subjects considered to have COPD in the BOLD 2005 study, (from a total

community-based sample of 847 subjects) were available for study, and vital status was obtained on the remainder. The first task was to correctly categorise subjects according to whether they had suffered at least one episode of pulmonary TB. Since history alone was likely to be insensitive, a method combining history and chest CT scans was developed, which is discussed in detail below. On the basis of this assessment, two categories could be confidently established: definite previous tuberculosis (DPTB) and no previous tuberculosis (NPTB). Another category, probable previous tuberculosis (PrPTB), comprised subjects with CT-scan features compatible with PPTB but no history of this infection. In some analyses, DPTB and PrPTB were combined, and are referred to as PPTB.

11.2. Major findings: mechanism of airflow obstruction and structure-function relationships

The analyses of lung physiology and its relationship to quantitative lung imaging for the three categories of subjects provided evidence of significant differences not attributable to severity of COPD, and insights into potential mechanisms of disease.

Subjects with PPTB did not differ in terms of smoking history, MRC dyspnoea score, health status measured by the St George's Respiratory Questionnaire, presence of chronic bronchitis, mean FEV1, FVC or FEV1:FVC, or bronchodilator responsiveness. Additionally, their mean total lung capacity, vital capacity, residual volume and RV:TLC was similar to that in usual COPD.

However, despite these similarities, subjects with PPTB had a lower inspiratory capacity (IC), and a higher functional residual capacity (FRC) and expiratory reserve volume (ERV) than usual COPD, which suggests more static gas trapping – the median IC as a percentage of predicted, was 22.2% lower. Other physiological evidence of hyperinflation did not accompany these changes. The TLC in subjects with PPTB was no different from that in NPTB (median of 102.0% predicted in both), and RV and RV:TLC were

elevated to a similar extent in both (median RV 139.0% predicted median RV:TLC 55.5% for DPTB; and 133.0% predicted and 51.0% respectively for NPTB). These values also confirm that the presence of PPTB did not result in a restrictive defect, as might be expected with widespread or diffuse fibrosis. Indeed, the overall fibrosis score on CT scan was not increased, and volume loss and increased fibrosis score was only present in the right upper lobe (RUL). This volume loss, expressed as percentage of whole lung, reflects the known tendency for PTB to affect this lobe, and was not seen in the left upper lobe (LUL). Although pulmonary fibrosis is a hallmark of healed tuberculosis, apart from the RUL, none of the other lobes showed increased fibrosis scores in PPTB.

Compatible with the physiology findings, lung imaging revealed important differences between subjects with and without PPTB. First, more gas trapping was found in PPTB, while increases in emphysema score were of questionable significance. The gas trapping score corrected for the presence of emphysema was approximately 6.5% higher in subjects with DPTB, and 5.6% higher in PrPTB. Consistent with this; total lung density at full expiration was significantly lower in PPTB than in NPTB. In contrast, although emphysema score in subjects with DPTB was 3.5% higher, no increase was seen in PrPTB, which suggests that this finding should be interpreted with caution. Thus, on balance, gas trapping, which is usually a feature of pathology in bronchi and bronchioles, is the major functional abnormality. It is, however, important to note that the only imaging measurement of the bronchial tree, the Pi10, failed to confirm differences between subjects with and without PPTB. Potential reasons for this are discussed below.

A further difference in the lung physiology was the lower diffusing capacity (DL_{CO}) observed in subjects with PPTB (16.3% predicted lower for DPTB). This novel observation was evident in both univariate and multivariate analyses, and for both DPTB and PrPTB. The values for DL_{CO} were 61.7% predicted and 68.6% predicted for DPTB and PrPTB, respectively, compared

with 79.5% predicted for NPTB. The reasons for the lower DL_{CO} in subjects with PPTB require explanation.

A reduction in DL_{CO} is a feature of emphysema, and is negatively associated with the presence of low attenuation areas on HRCT. Putative responsible mechanisms are: ventilation perfusion abnormalities and loss of alveolar-capillary interface (gas-exchanging areas) in the lungs. Emphysema is unlikely to be the dominant mechanism of reduced DL_{CO} in the subjects in the present study, as the emphysema scores were generally low, and the higher emphysema scores seen in DPTB but not in PrPTB were inconsistent in various analyses. Moreover, the quantitative algorithm used to assess low-attenuation areas includes abnormal air spaces and cavities, which are common in healed PPTB, with the potential of falsely elevating emphysema scores in DPTB.

A more likely cause of reduced DL_{CO} is involvement of either the pulmonary vasculature, or bronchioles with resultant ventilation:perfusion mismatch. Pulmonary TB is known to cause profound changes in the pulmonary vasculature, and unlike usual COPD, post-tuberculous scarring is more frequently associated with the development of pulmonary hypertension and cor pulmonale.[206,207] Although vascular involvement (attenuation of pulmonary vasculature) could account for both the reduction in DL_{CO} and lower lung density observed on expiratory CT scans in PPTB, this mechanism does not explain the presence of CAO and reduced IC. These are best explained by gas trapping due to narrowing and obliteration of small and medium airways, typical of a bronchocentric process. This explanation is compatible with the site of disease described during the active phase of TB, where 95% of individuals display lesions in and around the small airways (e.g. 'tree-in-bud' or centrilobular nodules).[141] Although most of these lesions disappear after five months of treatment, healing may result in cicatricial fibrosis and narrowing or obliteration of bronchi or bronchioles. In this scenario, the reduced DL_{CO} may be the result of ventilation:perfusion mismatching, analogous to that observed in other diseases (e.g. idiopathic pulmonary fibrosis). It is also plausible that, after an episode of tuberculosis,

the peri-bronchiolar cicatricial fibrosis involves not only the airways, but also the adjacent vessels, with resultant loss of vascular bed. Thus, the combined involvement of smaller airways and vasculature, and subsequent obliteration of these structures that are below the limits of detection of even high-resolution CT scans, are proposed as the major site of disease in CAO following PPTB and the cause of the observed functional abnormalities.

Bronchiectasis in large airways is another feature of healed PTB. Although associated with CAO, the mechanisms responsible for this are unclear.[54] The results of the present study suggest that abnormalities in airways distant from the most scarred lobes are responsible for the functional abnormality. On lung imaging, no relationship between fibrosis scores and gas trapping was observed. Most gas trapping was seen in the lower lobes, while the highest fibrosis score was in the RUL. This is also supported, albeit weakly, by the negative findings of the Pi10 analysis. As discussed earlier, the Pi10 is based on measurements from the first few generations of airways, while the likely small airways are located more distally to the measured bronchi. A further limitation of the measurement is that the Pi10 references wall thickness to bronchial lumen area; thus, airways that are both dilated and thickened may appear to be 'normal'.

It is thought that this is the first study to report the differences in lung physiology and radiology between subjects with COPD and those with CAO associated with PPTB, which have been termed tuberculosis-associated obstructive pulmonary disease (TOPD).

11.3. The efficacy of treatment in TOPD

To determine the potential effect, if any, of medication on the lung physiology of subjects with PPTB and CAO, a two-week trial of prednisone and formoterol (LABA) was administered. No significant differences in the improvement of lung physiology parameters were demonstrated, including: pre-bronchodilator FEV1, or symptoms of dyspnoea (MRC Dyspnoea score) between subjects with PPTB or usual COPD. Both groups showed no

improvement in median dyspnoea scores, and only small changes in pre-bronchodilator FEV1 (70 mL for PPTB and 90 mL for NPTB). These findings accord with previous COPD studies that have demonstrated non-significant increases in FEV1 after administration of prednisone (20 mg/day for four weeks),[208] and, unlike asthma, the underlying pathological mechanisms of CAO associated with PPTB do not appear to respond to such short courses of therapy. Whether subjects with PPTB will demonstrate responses to longer-term medication, similar to those observed in usual COPD, is unknown and requires further investigation.

11.4. Diagnosing previous pulmonary tuberculosis

Central to the evaluation of the relationship between PPTB and CAO was the need to establish whether subjects had had pulmonary TB in the past. It was recognised that patient history would provide a falsely low estimate of this,[26] the effect of which would be to reduce the likelihood of detecting differences between COPD and TOPD. Thus, in this study, additional methods were used to attempt a more accurate estimation of PPTB. Chest X-rays proved to be of little additional value and the comparison with history was inconsistent; many with a history of TB had no radiographic changes, and others with changes on chest X-ray suggestive of PPTB gave no compatible history. On the other hand, CT imaging confirmed changes compatible with PPTB in almost all subjects with a positive history but, in addition, suggested PPTB in a further significant number of subjects. For the purposes of the present study, these were labelled as probable PPTB (PrPTB).

The high proportion of subjects in the PrPTB group may at first seem to be improbable, and this requires further discussion. Were the CT abnormalities in these subjects correctly assigned as PPTB, or did they represent other pathology such as: previous pneumonia, post-infectious bronchiectasis, pneumoconiosis, or the ‘dirty lungs’ (respiratory bronchiolitis) associated with heavy tobacco usage? First, it should be noted that the prevalence of PPTB in the Ravensmead and Uitsig suburbs has been well

studied and is known to be very high. For example, the self-reported history of PPTB in the Lung Health Study in 2002 was around 10% of the total adult population, and the incidence of PTB estimated at 776/100 000.[29] Furthermore, in this community, between 70% and 84% of people over the age of 15 years have a positive tuberculin test.[120] Thus, it is plausible that the majority of subjects has more than merely latent TB, but in fact has had at least a primary infection, with some resultant CT evidence of a node or scar. If this is true, it is also worth noting that in the majority of subjects with PrPTB that the abnormalities seen on CT scan were fairly minor. Thus, the differences in structure and function between PPTB groups and usual COPD may not be entirely due to the lesions of pulmonary TB directly, but due to a more subtle relationship between PTB and the development of CAO. A possibility is that there is potentiation or synergy between the effects of cigarette smoke and PPTB in the development of CAO, owing to persistence of antigen or organisms in healed or latent TB infection. Such mechanisms might result in the development of COPD in parts of the lung indirectly affected by TB. The present study was not able to address this possibility, which would require demonstration that CAO associated with PPTB is more severe and extensive than that in patients with similar smoking profiles. This deserves further study, and may cast light upon the poorly understood issue in COPD research – that of varying susceptibility. It remains unclear why some smokers develop COPD, but that the majority does not; it is plausible that persistent lung or airway inflammation from latent or PPTB may serve as a progression factor in this process.

The alternative explanation for the CT changes not associated with a history of PPTB is the lack of specificity of images obtained. This is likely in at least a proportion of the subjects in the PrPTB group, but there are several reasons for suggesting that this proportion may be small. First, the CT appearance of the alternative lung diseases mentioned above tend to be distinctive, and are unlikely to be confused with those of PPTB. Second, the radiologists who viewed the CT scans were experienced in the assessment of PTB (great experience in high-prevalence regions), and their concordance

for these 34 subjects with PrPTB was high (74%), as was their individual rating of confidence in their own assessments [see page 135 and Table 48].

Another explanation for the absence of a history of PTB in subjects with CT changes compatible with PPTB include: failure to recall a disease event, particularly if it occurred in childhood, or thorough denial (deliberate or instinctive), potentially because of stigma or embarrassment. Furthermore, episodes of subclinical disease may have healed spontaneously or following the use of mildly tuberculostatic antibiotics (e.g. fluoroquinolones), or may have been considered at the time to be pneumonia or a different chest disease.

In support of the accuracy of the PPTB classification system developed for the present research is the fact that, for most structure/function endpoints, the PrPTB group was intermediary to the NPTB and DPTB groups, which implies a gradation of disease severity.

11.5. Assessment of the BOLD method: questionnaires

To date, the BOLD method has been used to estimate and compare the prevalence of COPD in 31 sites on five continents, and studies in more countries are currently underway.[209] The present study is the first to interrogate the accuracy and diagnostic performance of the BOLD method. It was assessed in several ways: first, a measure of the performance of the BOLD questionnaires was assessed by comparing responses to selected questions in 2010 with those obtained five years earlier. Second, the performance of handheld spirometry using the EasyOne ndd spirometer was evaluated by comparing results of two assessments with the same spirometers at visits approximately two weeks apart. Additionally, these spirometer results were compared with those obtained concurrently (i.e. the same visit), using office spirometry equipment with accepted accuracy. Finally, the accuracy of the BOLD method for diagnosing COPD was evaluated by individual assessment of patients diagnosed with COPD in 2005.

The assessment of the BOLD questionnaire involved using questions, the responses to which should not have changed between the 2005 and 2010 studies. The correlation between responses to the questions on medical conditions and smoking status obtained in 2005 and 2010 appeared to be good (kappa values ranged from 0.74-1.00). However, there was surprising variability in the reporting of the subjects' own, as well as their fathers' levels of education. The reasons for this are unclear, but might simply reflect poor knowledge or recall of this detail. The general levels of education in the study community were very low, and these questions may have been regarded as unimportant.

The performance of questions related to PPTB was also assessed in the present study by comparison of results obtained using a more-comprehensive set of questions. As discussed above [page 141], the conclusion was that the current BOLD questions performed adequately for confirming the presence of PPTB.

11.6. Assessment of the BOLD method: spirometry

The BOLD method prescribes a handheld spirometer (i.e. EasyOne ndd spirometer, Medical Techonologies, Andover, USA) to assess lung function because of its suitability for use in subjects' homes, thus avoiding the need for attendance to study sites or clinics. Concerns could be raised about the performance of portable handheld spirometers, with possible sources of inaccuracy being: the performance of the equipment, the subject and the operator. In both the 2005 and 2010 study, experienced, fulltime pulmonary technologists with years of experience performed the spirometry, observed all guideline requirements for optimal performance of spirometry and recorded the reproducible values. A minority of potential subjects was unable to provide acceptable quality flow volume loops; therefore, their spirometry was not included in the analysis. In the 2010 survey, the same technologists, using the same spirometers that were used in 2005, performed the tests. However, large differences in the results for both FEV1 and FVC

were found between visits conducted a mean of 10.8 days apart, but no consistent pattern suggesting a systematic error was evident. For FEV1, differences of more than 150 mL in either direction were observed in 28.6% of subjects, and FVC differed by more than 150 mL in 66.1% of subjects. Using these values, the presence or absence of CAO changed between visits in 19.6% (11 of 56) of subjects.

As a further check of the EasyOne ndd performance, at Visit 2, spirometry was performed first with the EasyOne ndd and then, within minutes, with an office (Nspire, Ferraris, Columbia, USA) spirometer; this revealed a similar inconsistency of results. The FEV1 differed by more than 150 mL between the spirometers in 22.5% of subjects (23 of 102), with handheld values differing by up to 250 mL below or 333 mL above corresponding office spirometer measurements, and the designation of CAO (presence or absence) changed in 16.7% of subjects (17 of 102).

Thus, there was considerable variation in the reproducibility of handheld spirometer measurements, and large differences when compared to office spirometry; these differences appeared to be random (i.e. not systematic or unidirectional). Since the performance of the Nspire was not tested in a similar manner, comparison of the performance of the two spirometers was not possible. However, the results of these assessments support concerns about the accuracy of the assessment of CAO using the EasyOne nnd spirometer, and basing the diagnosis of COPD on a single measurement performed with this equipment. Possible solutions might be to ensure that the measurement is repeated at a second visit to the subject's home, or simply to accept and allow for uncertainty in the estimates of COPD diagnosed using the BOLD criteria. While suitable for epidemiological/population-level research, the EasyOne ndd performance may not be acceptable for use in clinical practice for the diagnosis and management of individual patients.

11.7. Assessment of the BOLD method: misdiagnosis

A second concern regarding the BOLD method is the assumption that all subjects with CAO have COPD. This assumption is based on the likelihood that COPD is the most prevalent cause of post-bronchodilator CAO (as opposed to reversible airflow obstruction seen in asthma) in adults aged 40 years and older. However, there is no correction for potential misclassification, nor have there been studies that estimate the prevalence of misdiagnosis. It is well recognised in adult patients that asthma and other less-common diseases, like bronchiectasis, may also be associated with chronic fixed airflow obstruction. Therefore, although the risk of misdiagnosis is reduced by restricting surveys to persons aged 40 years and older, and, in the case of asthma, by measuring spirometry after bronchodilator, misdiagnosis is inevitable. The BOLD method does not provide a recommendation concerning the need to identify possible asthma by other means (e.g. trial of treatment), nor to estimate the magnitude of misdiagnosis. As a result, BOLD estimates of burden of COPD are likely to be falsely high, which when applied to large populations, may result in serious exaggerations of the extent of the problem. The present study provided a unique opportunity to assess the diagnostic accuracy of the BOLD method by retrospectively confirming the diagnosis of COPD, and by determining the prevalence of asthma.

Five years after the initial Cape Town BOLD 2005 study, it was found that 15.1% of subjects (16 of 106) no longer demonstrated CAO, when using the fixed-ratio definition (i.e. FEV1:FVC ratio <0.7). When the lower limit of normal (LLN) definition was employed, this increased to 25.5% (27 of 106), which confirmed the well-described tendency of the fixed ratio to over-diagnose CAO in the elderly. Of the 11 subjects having CAO, as defined by fixed-ratio but not LLN definition, nine were over 65 years (82.0%), seven over 70 years (64.0%) and five over 75 years of age (46.0%).

The possibility that the improvement seen in some subjects in 2010 was the result of treatment for COPD received between surveys is unlikely for

several reasons. First, although commencing COPD long-acting bronchodilators such as tiotropium and long-acting beta2-agonists improves airflow limitation, the ratio of FEV1:FVC improves in only a small proportion, as improvements in both FEV1 and FVC occur together in most. Second, improvements in CAO tend to last for only a few months or years, but by five years CAO should again be evident.[68,69] Third, only a minority of subjects in this cohort had received long-acting bronchodilators (3.7%). Furthermore, a drug-withhold period was observed before Visit 2 and, in spite of this, there was no increase in the proportion of subjects with CAO at this visit.

After developing and applying different definitions for asthma and specialist review, the confidence limits for a diagnosis of asthma in the Follow-up cohort was estimated to be between 10.4%-17.9%. When only subjects with post-bronchodilator airflow obstruction at Visit 1 were included (n=90), the estimates of asthma prevalence were between 11.1%-18.8%, and that for subjects without obstruction (n=16) was between 6.3%-18.8%. It should be noted that, in the whole Follow-up cohort, the proportion of subjects with clinical asthma was similar (approximately 15.0%) in those with CAO to those without. Thus, the presence of asthma did not account for the over-diagnosis of CAO in BOLD 2005. Of those labelled as asthma, and having both CAO and a smoking history, some may be considered as asthma-COPD overlap syndrome (ACOS). However, even if this diagnosis is made, these subjects will require a treatment approach different to COPD without features of asthma.[98]

This estimate of 15.0% (with confidence limits from 10.0%-18.0%) may prove useful as a correction to apply to results obtained in BOLD studies in other sites, recognising that the prevalence of asthma in adults might vary in different populations surveyed, and additionally, that asthma with CAO may be higher in populations where asthma is under-diagnosed and poorly treated, which will apply in some, but not all, BOLD sites.

Importantly, as the entire BOLD 2005 cohort was not studied, the analysis only considered potential over-diagnosis in the BOLD method, and

does not inform on those falsely designated as normal (i.e. no airflow obstruction) during that survey.

11.8. Natural history of COPD

Bearing in mind the above findings and limitations, follow-up of the BOLD cohort permitted an assessment of the natural history and outcome of patients diagnosed as COPD in 2005. Of the 196 eligible subjects diagnosed as COPD in 2005, almost a quarter (23.0%) died in the subsequent five years. More than half (58.0%) of these deaths occurred in subjects with only mild or moderate COPD in 2005 (i.e. GOLD stage 1/2 disease). The cause of death was cardiovascular in 22.0% and respiratory in 18.0%, but unknown in 47.0%. On multivariate analysis, only older age and severe COPD (GOLD stage 4 disease) predicted mortality. Previous pulmonary TB was not identified as a risk factor for mortality. These results are consistent with known associations in COPD, namely: a high five-year mortality due not only to respiratory disease, but also to cancer and cardiovascular causes.[210] However, the small size of the present cohort and limited details of causes of death do not permit meaningful comparisons.

Significantly, particularly in the African context, it can be confirmed that none of the patients who were screened or enrolled tested positive for HIV (an exclusion criteria). This may be attributable to several factors: first, the cohort comprised of older subjects (>40 years in 2005), in which HIV is less common. Second, Ravensmead/Uitsig is a relatively stable community, which may be a barrier to the usual drivers of HIV transmission, namely multiple concurrent and sequential sexual partners. Third, a selection bias may have occurred, with subjects who were HIV positive in 2005 (HIV status was not assessed during that survey) more likely to have died. However, the analysis of causes of death from the death registry gave no indication of this.

COPD is considered to be a progressive disease, with lung function declining at rates higher than that associated with normal aging, even after smoking cessation. The 2010 study provided the opportunity to study

change in lung function (FEV1, FVC and FEV1:FVC ratio) over five years. The median decline in FEV1 in the whole 2005 cohort was 28.9 mL/yr, but this did not exceed the predicted age-related decline. Moreover, there was no difference in the rate of decline between the four GOLD stages of severity. Similarly, no difference was observed between those with and without a previous history of TB. However, these results should be viewed with circumspection, as the numbers in each group were small and heterogeneity was large.

The decline in FVC was similar to that of the FEV1: in the whole cohort, a median decline over five years was 75 mL (or 15 mL/yr), which, expressed as percentage of predicted, was not greater than the age-related decline. However, the decline in FVC was greater in subjects with GOLD stage 1 disease, both expressed in ml and as percentage of predicted, compared to GOLD stage 2 and 3 disease (–80 mL and –140 mL, respectively, $p<0.01$ versus stage 1). This finding is in keeping with other studies demonstrating more rapid lung function decline (both FEV1 and FVC) in earlier stages of COPD.[64]

The analysis of changes in stage of GOLD severity revealed that the majority (55.0%) of subjects remained in the same stage, 20.0% (16 subjects) worsened and 26.0% (27 subjects) improved to a milder stage. Some, but not all, of the improvement was accounted for by those who were no longer obstructed at follow-up. Together, these findings suggest a rather more benign course of chronic airflow obstruction in this cohort, bearing in mind that this was a 'survivor' population and that many, possibly with more aggressive disease, may have died, as well as the small numbers studied.

11.9. Strengths and limitations of this study

The design of the present study has several strengths and unique features. First, the study population represented the whole cohort of subjects found to have CAO in a well-structured community-based survey and, therefore, reflects the spectrum and prevalence of CAO in that community, including

disease severity and risk factors. Second, its longitudinal nature, employing the same methods (questionnaires, lung function tests and apparatus) as in the initial survey ensured a level of accuracy and permitted analyses not possible in cross-sectional surveys. Third, to our knowledge this is one of the first follow-up studies of patients identified with CAO in BOLD studies. Thus it provides a comprehensive evaluation of both the BOLD methods and a detailed assessment of the subjects identified with CAO resulting in accurate diagnoses. In the analysis of risk factors for CAO, and particularly the role of PPTB, the relative homogeneity of the population with respect to environmental exposures, living conditions and socioeconomic status, removed some variables. Thus, although not of case-control design, multivariate analyses could be used to identify determinants of disease. Further, the fortuitous division of the cohort into three groups of interest: no PPTB, probable PPTB and definite PPTB, permitted meaningful analyses in spite of the relatively small numbers.

Several limitations of the study are acknowledged: first, the small size of the study cohort. Second, the limited response rate: only 107 of 196 potential participants (54.6%) were included, but limited information was available on the 45 (23.0%) that had died. The deaths are assumed to have had a significant impact on the assessment of decline in lung function. However, as far as could be ascertained, with the exception of those that had died, the subjects studied were representative of those not included. A further weakness of the study is the method used to decide the presence of PPTB; this is fully discussed above. Additionally, the studies were conducted in persons not co-infected with HIV, and it is unclear whether PTB in HIV will be associated with the development of COPD. Finally, the significant methodological limitations of the measures of wall thickness and in the assessment of gas trapping (the corrected gas trapping score) may have influenced the results and conclusions concerning structure/function relationships in COPD and TOPD.

11.10. Application of research findings and recommendations

The research presented has several important potential applications:

1. The development of the BOLD method, which for the first time has enabled comparisons of the burden of COPD in different countries, has provided valuable information concerning this disease. These are described in more than 40 publications in the scientific literature. To date, criticism of the BOLD method has focused on the use of FEV1:FVC ratio <0.7 rather than the more scientifically correct 'lower limit of normal' definition to identify CAO. However, this study has identified additional and significant sources of error in the BOLD estimates. First, in the non-reproducibility of a single measurement of post-bronchodilator FEV1 and the confounding influence of asthma. It is suggested that estimates of COPD based on BOLD should assume over-diagnosis and adjust the estimates downward by approximately 15.0%. This adjustment may be relevant to planners of health services, recognising that asthma treatments are highly effective and that the prognosis is better than in COPD.
2. Tuberculosis-associated obstructive pulmonary disease (TOPD) should be recognised as a distinct phenotype of COPD. This recognition would have several potential benefits:
    a. It would increase the urgency of controlling TB and tobacco-use as public health priorities.
    b. It would encourage recognition of this condition in other countries. Since TB remains common not only in Africa but also in India, China and other countries with large populations, TOPD is highly relevant and may prove to be the most common chronic lung disease in adults. It is likely to be responsible for considerable global morbidity and mortality.
    c. It would lead to trials of treatment for this condition. Preliminary data from the present research failed to confirm short-term benefit of either formoterol (bronchodilator) or oral

corticosteroids on lung function or symptoms. Other COPD treatments require formal evaluation for this indication.

d. It would focus attention on the mechanisms of disease and the potential for developing treatments that target these mechanisms. Phenotyping patients with COPD is being proposed as a means of guiding selection of treatment and the development of novel treatments that target relevant mechanisms of disease. This may be done for TOPD.
e. It would lead to further research on how to arrest disease progression, as the effect of PPTB may not be temporary and limited. The concept of persisting tuberculosis antigen or inflammation influencing the development of COPD in those who smoke and/or are exposed to other risk factors, such as environmental or workplace atmospheric pollution, warrants further study.
f. Relevant to countries with high prevalence of HIV infection, research is required on the long-term effects on the lungs of combined infection with TB and HIV. Preliminary research has confirmed impaired gas transfer and, possibly, also the premature development of CAO in HIV. It is likely that PTB may be an aggravating factor in such populations.

Despite intense research and public health efforts, the TB epidemic in South Africa continues unabated, and the lifetime risk of infection remains high. The finding that even unrecognised infection with *Mycobacterial tuberculosis*, with minimal evidence of residual abnormality on lung imaging, is a risk factor for physiological consequences (impaired lung function) raises the prospect of a heavy burden of chronic lung disease being attributable to TB infection. This is the likely explanation for the record levels of CAO observed in the Cape Town BOLD cohort. Although the burden of TOPD in other provinces of South Africa has yet to be established, the findings described in this study are sufficient to cause alarm and be translated into practice and policy.

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Appendices

Appendix 1 – BOLD Core Questionnaire

Country Code ____ ____ ____ 1

City Code ____ ____ 2

ID ____ ____ ____ ____ ____ ____ 3

Date: ____ ____/____ ____/____ ____ ____ ____ 4-9
d d m m y y y y

BOLD CORE QUESTIONNAIRE

Demographics

1. *What is the participant's sex?* Male ☐ 1 7
Female ☐ 2

2. What is your race? _____ ___ ___ ___ 8

3. What is your date of birth? ____ ____/____ ____/____ ____ ____ ____ 9-11
d d m m y y y y

4. How many years of schooling have you completed? ___ ___ 12

5. What is the highest level of schooling you have completed? Primary School ☐ 1 13
Middle School ☐ 2
High School ☐ 3
Some College (Trade/Professional/Community) ☐ 4
Four-Year College/University ☐ 5
None ☐ 6
Unknown ☐ 7

6. What is the highest level of schooling your father has completed? Primary School ☐ 1 14
Middle School ☐ 2
High School ☐ 3
Some College (Trade/Professional/Community) ☐ 4
Four Year College/University ☐ 5
None ☐ 6
Unknown ☐ 7

Respiratory Symptoms and Disorders

These questions pertain mainly to your chest. Please answer yes or no if possible. If you are in doubt about whether your answer is yes or no, please answer no.

Cough

7. Do you usually cough when you don't have a cold? Yes ☐ 1 15
No ☐ 2

[If yes, continue with Question 7A; If no, skip to Question 8]

7A. Are there months in which you cough on most days? Yes ☐ 1 16
No ☐ 2

[If yes, ask both Questions 7B & 7C; If no, skip to Question 8]

7B. Do you cough on most days for as much as three months each year? Yes ☐ 1 17
No ☐ 2

7C. For how many years have you had this cough? Less than 2 years ☐ 1 18
2-5 years ☐ 2
More than 5 years ☐ 3

Phlegm

8. Do you usually bring up phlegm from your chest, or do you usually have phlegm in your chest that is difficult to bring up when you don't have a cold? Yes ☐ 1 19
No ☐ 2

[If yes, continue with Question 8A; If no, skip to Question 9]

8A. Are there months in which you have this phlegm on most days? Yes ☐ 1 20
No ☐ 2

[If yes, ask both Questions 8B & 8C; If no, skip to Question 9]

8B. Do you bring up this phlegm on most days for as much as three months each year? Yes ☐ 1 21
No ☐ 2

8C. For how many years have you had this phlegm? Less than 2 years ☐ 1 22
2-5 years ☐ 2
More than 5 years ☐ 3

Wheezing/Whistling

9. Have you had wheezing or whistling in your chest at any time in the last 12 months? Yes ☐ 1 23
No ☐ 2

[If yes, ask both Questions 9A & 9B; If no, skip to Question 10]

9A. In the last 12 months, have you had this wheezing or whistling only when you have a cold? Yes ☐ 1 24
No ☐ 2

9B. In the last 12 months, have you ever had an attack of wheezing or whistling that has made you feel short of breath? Yes ☐ 1 25
No ☐ 2

Breathlessness

10. Are you unable to walk due to a condition other than shortness of breath? Yes ☐ 1 26
No ☐ 2

[If yes to Question 10, please describe this condition on the line below and then skip to Question 12. If no, go directly to Question 11.]

Nature of condition(s): _____

11. Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill? Yes ❑ 1 27 / No ❑ 2

[If yes, ask Question 11A through 11D; If no, skip to Question 12]

11A. Do you have to walk slower than people of your age on level ground because of shortness of breath? Yes ❑ 1 28 / No ❑ 2 / Does not apply ❑ 3

11B. Do you ever have to stop for breath when walking at your own pace on level ground? Yes ❑ 1 29 / No ❑ 2 / Does not apply ❑ 3

11C. Do you ever have to stop for breath after walking about 100 yards (or after a few minutes) on level ground? Yes ❑ 1 30 / No ❑ 2 / Does not apply ❑ 3

11D. Are you too short of breath to leave the house or short of breath on dressing or undressing? Yes ❑ 1 31 / No ❑ 2 / Does not apply ❑ 3

12. Has a doctor or other health care provider ever told you that you have emphysema? Yes ❑ 1 32 / No ❑ 2

13. Has a doctor or other health care provider ever told you that you have asthma, asthmatic bronchitis or allergic bronchitis? Yes ❑ 1 33 / No ❑ 2

[If yes, ask Question 13A. If no, skip to Question 14]

13A. Do you still have asthma, asthmatic bronchitis or allergic bronchitis? Yes ❑ 1 34 / No ❑ 2

14. Has a doctor or other health care provider ever told you that you have chronic bronchitis? Yes ❑ 1 35 / No ❑ 2

[If yes, ask Question 14A. If no, skip to Question 15]

14A. Do you still have chronic bronchitis? Yes ❑ 1 36 / No ❑ 2

15. Has a doctor or other health care provider ever told you that you have chronic obstructive pulmonary disease (COPD)? Yes ❑ 1 37 / No ❑ 2

Management Section

Now I am going to ask you about medicines that you may be taking to help with your breathing. I want to know about medicines that you take on a regular basis and medicines that you may take only for the relief of symptoms. I would like you to tell me each medicine that you take, what form do you take it in, and how often you take it each month.

16. In the past 12 months, have you taken any medications for your breathing (including medications for nasal congestion)? Yes ❑ 1 38 / No ❑ 2

If participant does not take any medications to help their breathing, skip to Question 17.

16A.Medication Name (not entered)							
16B.Medication Code	___ ___ ___ 39	___ ___ ___ 44	___ ___ ___ 49	___ ___ ___ 54	___ ___ ___ 59	___ ___ ___ 64	___ ___ ___ 69
16C.Formulation	Pills ❑1 Inhaler ❑2 Nebulizer ❑3 Liquid ❑4 Suppository ❑5 Injection ❑6 Other ❑7	Pills ❑1 Inhaler ❑2 Nebulizer ❑3 Liquid ❑4 Suppository ❑5 Injection ❑6 Other ❑7	Pills ❑1 Inhaler ❑2 Nebulizer ❑3 Liquid ❑4 Suppository ❑5 Injection ❑6 Other ❑7	Pills ❑1 Inhaler ❑2 Nebulizer ❑3 Liquid ❑4 Suppository ❑5 Injection ❑6 Other ❑7	Pills ❑1 Inhaler ❑2 Nebulizer ❑3 Liquid ❑4 Suppository ❑5 Injection ❑6 Other ❑7	Pills ❑1 Inhaler ❑2 Nebulizer ❑3 Liquid ❑4 Suppository ❑5 Injection ❑6 Other ❑7	Pills ❑1 Inhaler ❑2 Nebulizer ❑3 Liquid ❑4 Suppository ❑5 Injection ❑6 Other ❑7
16D.Is the Medicine taken on most days, or just when you have symptoms, or both? *(If 'most days' ask Q16E, if 'symptoms', ask Q16F, if 'both', ask both Q16E and Q16F.)*	Most Days ❑1 Symptoms ❑2 Both ❑3	Most Days ❑1 Symptoms ❑2 Both ❑3	Most Days ❑1 Symptoms ❑2 Both ❑3	Most Days ❑1 Symptoms ❑2 Both ❑3	Most Days ❑1 Symptoms ❑2 Both ❑3	Most Days ❑1 Symptoms ❑2 Both ❑3	Most Days ❑1 Symptoms ❑2 Both ❑3
16E. When you are taking the medication, how many days a week do you take it?	_____ days 42	_____ days 47	_____ days 52	_____ days 57	_____ days 62	_____ days 67	_____ days 72
16F. When you are taking the medication, how many months in the past 12 months have you taken it?	0-3 ❑1 43 4-6 ❑2 7-9 ❑3 10-12 ❑4	0-3 ❑1 48 4-6 ❑2 7-9 ❑3 10-12 ❑4	0-3 ❑1 53 4-6 ❑2 7-9 ❑3 10-12 ❑4	0-3 ❑1 58 4-6 ❑2 7-9 ❑3 10-12 ❑4	0-3 ❑1 63 4-6 ❑2 7-9 ❑3 10-12 ❑4	0-3 ❑1 68 4-6 ❑2 7-9 ❑3 10-12 ❑4	0-3 ❑1 73 4-6 ❑2 7-9 ❑3 10-12 ❑4

17. Please tell me about any other products that you take or things you do to help your breathing that you have not already told me about.

Medicine or Activity	*Code*
	___ ___ ___ 74
	___ ___ ___ 75
	___ ___ ___ 76
	___ ___ ___ 77

18. Has a doctor or other health care provider ever had you blow into a machine or device in order to measure your lungs (i.e., a spirometer or peakflow meter)? Yes ☐ 1 No ☐ 2 78

[If yes, ask Question 18A. If no, skip to Question 19]

18A. Have you used such a machine in the past 12 months? Yes ☐ 1 No ☐ 2 79

19. Have you ever had a period when you had breathing problems that got so bad that they interfered with your usual daily activities or caused you to miss work? Yes ☐ 1 No ☐ 2 80

[If yes, ask Question 19A. If no, skip to Question 20]

19A. How many such episodes have you had in the past 12 months? ___ ___ ___ episodes 81

[If 19A >0, ask Questions 19B and 19C, else skip to Question 20]

19B. For how many of these episodes did you need to see a doctor or other health care provider in the past 12 months? ___ ___ episodes 82

19C. For how many of these episodes were you hospitalized overnight in the past 12 months? ___ ___ episodes 83

[If 19C >0, ask Question 19C1, else skip to Question 20]

19C1. All together, for how many total days were you hospitalized overnight for breathing problems in the past 12 months? ___ ___ ___ days 84

Tobacco Smoking

Now I am going to ask you about smoking. First I will ask about cigarettes.

20. Have you ever smoked cigarettes? Yes ☐ 1 No ☐ 2 85

("Yes," means more than 20 packs of cigarettes in a lifetime or more than 1 cigarette each day for a year)

[If yes, ask questions 20A through 20D; otherwise, skip to Question 22)

20A. How old were you when you first started regular cigarette smoking? ___ ___ years old 86

20B. If you have stopped smoking, how old were you when you last stopped? (If the participant has not stopped smoking, record as code '99'.) ___ ___ years old 87

20C. On average over the entire time that you smoke(d), about how many cigarettes per day do (did) you smoke? ___ ___ ___ cigarettes/day 88

20D. On average over the entire time that you smoke(d), do (did) you primarily smoke manufactured or hand-rolled cigarettes? Manufactured ☐ 1 Hand-rolled ☐ 2 89

[If the participant currently smokes cigarettes (Question 20B is '99'), then ask Questions 21A and 21B. Otherwise, skip to Question 22]

21A. In the last year, how many times have you quit smoking for at least 24 hours? ___ ___ ___ times 90

21B. Are you seriously thinking of quitting smoking? Yes, within the next 30 days ☐ 1 Yes, within the next 6 months ☐ 2 No, not thinking of quitting ☐ 3 91

22. Have you ever smoked a pipe or cigar? Yes ☐ 1 No ☐ 2 92

[If yes, ask question 22A. If no, proceed to question 23]

22A. Do you now smoke a pipe or cigar? Yes ☐ 1 No ☐ 2 93

[If the participant has never smoked (answered "no" to both Questions 20 and 22), then skip to Question 25. Otherwise, proceed to Question 23]

23. Has a doctor or other health care provider ever advised you to quit smoking? Yes ☐ 1 No ☐ 2 94

[If yes, ask Questions 23A and 23B. If no, skip directly to Question 24]

23A. Have you received medical advice to stop smoking within the past 12 months? — Yes ❑ 1 / No ❑ 2 — 95

23B. Have you used any medication (prescription or non-prescription), including a nicotine patch, to help you stop smoking? — Yes ❑ 1 / No ❑ 2 — 96

[If yes, ask Question 23B1, then ask Question 24. If no, skip directly to Question 24]

23B1. What kind of medication did you take to help you stop smoking? — Nicotine Replacement ❑ 1 / Buproprion ❑ 2 / Tofranil ❑ 3 / Other ❑ 4 — 97

24. Have you used or done anything else to help you stop smoking? — Yes ❑ 1 / No ❑ 2 — 98

[If yes, ask Question 24A, otherwise skip to Question 25]

24A. What did you do? — Hypnosis ❑ 1 / Acupuncture ❑ 2 / Biofeedback ❑ 3 / Other ❑ 4 — 99

Occupational Exposure

25. Have you ever worked for a year or more in a dusty job? — Yes ❑ 1 / No ❑ 2 — 100

[If yes, ask Question 25A, otherwise skip to Question 26]

25A. For how many years have you worked in dusty jobs? ____ ____ years — 101

Additional Co-morbidities

26. Has a doctor or other health care provider ever told you that you had:

26A. Heart disease — Yes ❑ 1 / No ❑ 2 — 102

26B. Hypertension — Yes ❑ 1 / No ❑ 2 — 103

26C. Diabetes — Yes ❑ 1 / No ❑ 2 — 104

26D. Lung cancer — Yes ❑ 1 / No ❑ 2 — 105

26E. Stroke — Yes ❑ 1 / No ❑ 2 — 106

26F. Tuberculosis — Yes ❑ 1 / No ❑ 2 — 107

[If yes to 26F, then ask 26F1; otherwise, skip to Question 27]

26F1. Are you currently taking medicine for tuberculosis? — Yes ❑ 1 / No ❑ 2 — 108

[If no to 26F1, then ask 26F2; otherwise, skip to Question 27]

26F2. Have you ever taken medicine for tuberculosis? — Yes ❑ 1 / No ❑ 2 — 109

27. Have you ever had an operation on your chest in which a part of your lung was removed? — Yes ❑ 1 / No ❑ 2 — 110

28. Were you hospitalized as a child for breathing problems prior to the age of 10? — Yes ❑ 1 / No ❑ 2 — 111

29. In the past 12 months did you get a flu shot? — Yes ❑ 1 / No ❑ 2 — 112

30. Has a doctor or other health care professional told your father, mother, sister or brother that they had a diagnosis of emphysema, chronic bronchitis or COPD? — Yes ❑ 1 / No ❑ 2 — 113

31. Has anyone living in your home (besides yourself) smoked a cigarette, pipe or cigar in your home during the past two weeks? — Yes ❑ 1 / No ❑ 2 — 114

Appendix 2 – Additional Tuberculosis Questionnaire

ADDITIONAL TUBERCULOSIS QUESTIONNAIRE (PTbQ)

1 **Diagnosis of Chronic Lung Disease**:

1.1 Have you ever been told by a doctor that you have damaged lungs, smokers lungs, emphysema, chronic bronchitis, or COPD?

Yes ❑
No❑

1.2 Can you remember when you were first told of this?

__ __ __ __ (Y/Y/Y/Y)

2 **Have you ever been diagnosed with tuberculosis**?

Yes ❑
No❑

2.1 How many times have you been treated for tuberculosis?

..... times

2.2 THE EPISODE of TB:

Number .....

Complete Section 2.2 for **EACH EPISODE** of TB

2.2.1 When were you diagnosed as having tuberculosis?

_____(year)

2.2.2 What part of the body did the tuberculosis affect?

2.2.2.1 Lungs	Yes ❑ No❑
2.2.2.2 Glands	Yes ❑ No❑
2.2.2.3 Brain / Meninges (meningitis)	Yes ❑ No❑
2.2.2.4 Abdomen	Yes ❑ No❑
2.2.2.5Heart/ or heart sac	Yes ❑ No❑
2.2.2.6 Other part of the body:	Yes ❑ No❑

Please specify: .....

2.2.3 Were the doctors / clinic sure that you had tuberculosis

Yes ❑ No❑

2.2.4 Do you remember how they confirmed that you had tuberculosis? Was it diagnosed from

2.2.4.1 Sputum (phlegm)	Yes ❑ No❑
2.2.4.2 Chest X-ray	Yes ❑ No❑
2.2.4.3 Bone marrow	Yes ❑ No❑
2.2.4.4 Lumbar puncture	Yes ❑ No❑
2.2.4.5 Not sure	❑

2.2.4.6 Other .....

2.2.5 Did you ever stay in hospital for treatment of TB? (Y/N/Cant remember) Yes ❑ No❑ Can't remember ❑

2.2.5.1 How long for were you in the hospital (sleeping in the hospital)?

Less than 1 week ❑ 1 week to 1 month ❑ More than 1 month❑

2.2.6 Where did you get your pills or injections for TB (which clinic)?

.....

2.2.7 How long did you take treatment for? (For how many months)

.....months

❑cant remember

2.2.8 Did you finish the treatment? (Y/N/cant remember)

Yes ❑ No❑ Can't remember❑

2.2.9 Did you feel partly or completely well again (better) after ending treatment?

Yes ❑ No❑ Can't remember ❑

2.2.10 Did the clinic doctor say you were cured?

Yes ❑ No❑ Can't remember ❑

2.2.11 Did you stop attending the clinic before the treatment was meant to stop?

Yes ❑ No❑ Can't remember ❑

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PATIENT INFORMATION FROM CLINIC / HOSPITAL RECORDS

2.3 *THE EPISODE of TB:*

Number: .....

Complete Section 2.3 for **EACH EPISODE** of TB

2.3.1 Tuberculosis diagnosis confirmed? (Y/N)

2.3.1.1 On Xray Yes ❑ No❑

2.3.1.2 On Sputum Yes ❑ No❑

2.3.1.3 On Culture Yes ❑ No❑

2.3.1.4 On FNAB Yes ❑ No❑

2.3.1.5 Other .....

2.3.2 Subject received treatment? Yes ❑ No❑

2.3.3 Subject completed treatment? Yes ❑ No❑

2.3.4 Drug resistance confirmed? Yes ❑ No❑

Appendix 3 - St George's Respiratory Questionnaire

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
ORIGINAL ENGLISH VERSION

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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continued...

St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have had over the past 3 months.

Please tick (✓) one box for each question:

	most days a week	several days a week	a few days a month	only with chest infections	not at all
1. Over the past 3 months, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 3 months, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 3 months, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 3 months, I have had attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 3 months how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) one:

- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✓) one:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 3 months, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✓) one:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day is good ☐
- every day is good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✓) one:

- No ☐
- Yes ☐

continued...

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your chest condition?

Please tick (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✓) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

Section 2

Questions about what activities usually make you feel breathless <u>these days</u>.

Please tick (✓) in *each box* that applies to you *these days*:

	True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

Please tick (✓) in *each box* that applies to you *these days*:

	True	False
My cough hurts	☐	☐
My cough makes me tired	☐	☐
I am breathless when I talk	☐	☐
I am breathless when I bend over	☐	☐
My cough or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

Please tick (✓) in *each box* that applies to you *these days*:

	True	False
My cough or breathing is embarrassing in public	☐	☐
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

Please tick (✓) in *each box* that applies to you *these days*:

	True	False
My medication does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My medication interferes with my life a lot	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

Please tick (✓) in ***each box*** that applies to you ***because of your breathing:***

	True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
Jobs such as housework take a long time, or I have to stop for rests	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

Please tick (✓) in ***each box*** that applies to you ***because of your chest trouble:***

	True	False
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

continued...

St. George's Respiratory Questionnaire

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog
Doing things at home or in the garden
Sexual intercourse
Going out to church, pub, club or place of entertainment
Going out in bad weather or into smoky rooms
Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

.....
.....
.....
.....

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐
It stops me doing one or two things I would like to do ☐
It stops me doing most of the things I would like to do ☐
It stops me doing everything I would like to do ☐

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

Appendix 4 – Atopic Questionnaire

TOPD (V1) UCT Lung Institute TOPD Code No:_ _ _ Subject's initials:_ _ _

4.9. Information on allergic atopic diseases

4.9.1. Physician-based diagnosis of asthma ever been given? No ☐ Yes ☐

4.9.2. Personal history of asthma (particularly in childhood)? No ☐ Yes ☐

4.9.3. Periodic wheezing ever? No ☐ Yes ☐
- 4.9.3.1. Spontaneous ☐
- 4.9.3.2. Specific trigger (house dust, animals, parks, gardens, etc) ☐
- 4.9.3.3. Physical exercise ☐
- 4.9.3.4. Tobacco smoke and/or fumes ☐
- 4.9.3.5. Cold weather / changes in temperature ☐

4.9.4. Periodic cough ever? No ☐ Yes ☐
- 4.9.4.1. Spontaneous ☐
- 4.9.4.2. Specific trigger (house dust, animals, parks, gardens, etc) ☐
- 4.9.4.3. Physical exercise ☐
- 4.9.4.4. Tobacco smoke and/or fumes ☐
- 4.9.4.5. Cold weather / changes in temperature ☐

4.9.5. Periodic dyspnoea or chest tightness ever? No ☐ Yes ☐
- 4.9.5.1. Spontaneous ☐
- 4.9.5.2. Specific trigger (house dust, animals, parks, gardens, etc) ☐
- 4.9.5.3. Physical exercise ☐
- 4.9.5.4. Tobacco smoke and/or fumes ☐
- 4.9.5.5. Cold weather / changes in temperature ☐

4.9.6. Periodic wheezing, cough or dyspnoea in the past 12 months? No ☐ Yes ☐
- 4.9.6.1. Wheezing ☐
- 4.9.6.2. Cough ☐
- 4.9.6.3. Dyspnoea ☐

4.9.7. Physician-based diagnosis of allergic rhinitis ever been given? No ☐ Yes ☐

4.9.8. Personal history of allergic rhinitis? No ☐ Yes ☐

4.9.9. Bouts of nasal blockage, anterior rhinorrhoea and sneezing when not with a cold? No ☐ Yes ☐

4.9.10. Symptoms more intense during part of the year? No ☐ Yes ☐

Summer ☐ Autumn ☐ Winter ☐ Spring ☐

4.10. Other relevant information:

Appendix 5 – TOPD image acquisition protocol

CT Technique Chart for TOPD Imaging Study at Vincent Palotti Hospital for SIEMENS SENSATION 64 MDCT scanner
REVISED 2010-03-31

Shaded fields are user input fields on the scanner console. Other values are either calculated or derived from user inputs.

Techniques for Siemens Sensation 64 64-slice/0.37 sec	Helical – Full Chest at TLC **REQUIRED**	Helical – Full Chest at RV **REQUIRED**	Dynamic – TLC to RV
kV	120	120	120
Gantry Rotation Time	0.5 sec	0.5 sec	0.5 sec
mAs[1] (Regular patient-Large patient values)	40-60	40-60	25-40
Collimation (mm)	64x 0.6 mm collimation	64x 0.6 mm collimation	20x1.2 mm
Table incrementation (mm/rotation) – I	19.2 mm	19.2 mm	none
Detector Collimation (mm) – T	0.6 mm	0.6 mm	1.2 mm
Number of active channels – N	32	32	20
Detector Configuration – N x T	64 x 0.6 mm (Z flying focal spot)	64 x 0.6 mm (Z flying focal spot)	20 x 1.2 mm
Pitch ([mm/rotation] /beam collimation) – I/NT	1	1	0
Table Speed (mm/sec)	38.4 mm/sec	38.4 mm/sec	0
Scan Time (40 cm thorax)	11 sec	11 sec	Approx 20 sec
REQUIRED Reconstructed Thin Slice Width	1 mm	1 mm	2.4 mm
REQUIRED Thin Slice Reconstruction Interval	1 mm	1 mm	2.4 mm
REQUIRED Thin Slice Reconstruction Algorithm	B50f	B50f	B50f
REQUIRED # Images/Data set (40 cm thorax)	400	400	120

[1] – Siemens Scanners use the term "effective mAs" which is really [(mA*time)/Pitch]. Sites should enter the value in the effective mAs row at their scanner.

Definitions

T = Z axis collimation, or width of one data channel. In multi-detector CT scanners, several detector elements maybe grouped together to form one data channel.
N = # data channels, or the actual number of data channels used during an acquisition.
I = Increment, or the table increment *per rotation* of the x-ray tube in a helical scan.

Breath-Holding Instructions:

For the static TLC scan (Sequence #1), the participant is told to "Take your biggest breath in until you feel your lungs are completely full, in the same way you do in the lung function laboratory, and hold the breath." **For the RV Scan (Sequence #2)**, the patient should be coached with emphasis on instruction to blow all their air out. The participant should be told "to take another big breath in to fill up their lungs and then to blow all the air out as hard and fast a s possible without moving their body and then to squeeze all their air out until they feel that their lungs are completely empty and then they should signal that they are empty and hold their breath". This can be done by asking the patient to keep their toes apart at the beginning of the maneuver and to bring their toes together when they feel they are completely empty. At this stage, the technologist should remind the subjects to hold their breath for the entire scan and start the scan. **For the optional dynamic TLC to RV scan (Sequence #3)**, the patient is told to "Take a deep breath in until you feel your lungs are completely full, in the same way you do in the lung function laboratory, and hold the breath" The first image is acquired, and the patient is told to "breath out as hard and as fast as possible until you feel that your lungs are empty."

Appendix 6 – Additional Smoking Questionnaire

ADDITIONAL SMOKING QUESTIONNARE
TOPD STUDY

TOPD NO: .....
INITIALS: .....

Questionnaire performed by:.....

Date:.....

DOB:.....

AGE: ..... (calculated from DOB)

Do you/Have you ever smoked:

1. Cigarettes:
   i. Yes ☐ (go to page 2)
   ii. No ☐
2. Cannabis:
   i. Yes ☐ (go to page 3)
   ii. No ☐
3. Other (eg. Pipe tobacco, Mandrax, heroin) etc:
   i. Yes ☐ (go to page 4)
   ii. No ☐

- Description.....

ADDITIONAL SMOKING QUESTIONNARE
TOPD STUDY

TOPD NO: .....
INITIALS: .....

CIGARETTE SMOKING

1.1 Are you a:
1. Never Smoker? ☐ 2. Ex-smoker? ☐ 3.Current Smoker? ☐

1.2 Age started smoking: .....

1.3 Age stopped smoking (for the last time):..... *(use "99" is still smoking)*

Age	(Important events)	Number of Cigs per day	Number of Years	Pack Years
				(no.cig per day x No.of years/20)
<20				
20				
30				
40				
50				
60				
70				
80+				
			TOTAL	

ADDITIONAL SMOKING QUESTIONNARE TOPD NO: _____
TOPD STUDY INITIALS: _____

CANNABIS (Dagga) SMOKING

2.1 Are you a:

1. Never Smoker? ☐ 2. Ex-smoker? ☐ 3.Current Smoker? ☐

2.2 Age started smoking: .....

2.3 Age stopped smoking (for the last time):..... *(use "99" is still smoking)*

2.4 On average for this entire time period, how many cannabis joints did you smoke?

2.4.1.....joint per day 2.4.2.....joints per week

Age	(Important events)	Joints per week	Number of joints per day (Joints per week / 7)	Number of Years	Joint Years (no. Joints per day x No of years)
<20					
20					
30					
40					
50					
60					
70					
80+					
				TOTAL	

ADDITIONAL SMOKING QUESTIONNARE TOPD NO: _____
TOPD STUDY INITIALS: _____

OTHER .....(fill detail) SMOKING

3.1 Are you a:

1. Never Smoker? ☐ 2. Ex-smoker? ☐ 3.Current Smoker? ☐

3.2 Age started smoking: .....

3.3 Age stopped smoking (for the last time):..... *(use "99" is still smoking)*

3.4 On average for this entire time period, how many "units" joints did you smoke?

3.4.1....."units" per day 3.4.2....."units" per week

Define a "unit":..... (eg. Pipe of tobacco, pipe of crack)

Age	(Important events)	Units per week	Number of Units per day (Units per week / 7)	Number of Years	Unit Years (no. units per day x No of years)
<20					
20					
30					
40					
50					
60					
70					
80+					
				TOTAL	

Appendix 7 – Results of Clinical and Physiological Endpoints only for Subjects with Chronic Airflow Obstruction

Table 112: Comparison of the results of lung physiology at Visit 2 according to PPTB status, only in subjects in CAO.

(n=86)	NPTB	sd	PPTB	sd	*p-value*	*test*	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
(n)	(22)		(64)				(22)		(38)		(26)			
Post BD FVC (L) - mean	2.86	0.864	3.05	1.073	*0.464*	*t-test*	2.86	0.864	3.12	1.062	2.95	1.102	*0.619*	*ANOVA*
Post BD FVC (%) - mean	97.00	12.653	96.89	17.796	*0.978*	*t-test*	97.00	12.653	96.21	19.274	97.88	15.703	*0.9255*	*ANOVA*
Post BD FEV1 (L) -mean	1.66	0.621	1.63	0.760	***n/a***	***n/a***	1.66	0.621	1.63	0.804	1.63	0.707	***n/a***	***n/a***
Post BD FEV1 (L) - median	1.56	-	1.37	-	*0.6242*	*Wilcoxon*	1.56	-	1.40	-	1.31	-	*0.85*	*Kwallis*
Post BD FEV1 (%) -mean	69.55	17.896	65.08	23.383	*0.4165*	*t-test*	69.55	17.896	62.71	25.170	68.54	20.477	*0.4232*	*ANOVA*
Post BD FEV1:FVC - mean	0.58	0.112	0.53	0.128	***n/a***	***n/a***	0.58	0.112	0.51	0.130	0.56	0.121	*n/a*	*n/a*
Post BD FEV1:FVC - median	0.59	-	0.58	-	*0.135*	*Wilcoxon*	0.59	-	0.54	-	0.60	-	*0.1126*	*Kwallis*
Reversibility														
Litres - median	0.19	0.172	0.19	0.163	*0.7103*	*Wilcoxon*	0.19	0.172	0.15	0.150	0.20	0.183	*0.7168*	*Kwallis*
% change	12.22	12.583	12.63	16.696	*0.9055*	*Wilcoxon*	12.22	12.583	11.85	18.374	14.97	14.237	*0.8573*	*Kwallis*
Significant reversibility*														
Number of subjects	(9)	-	(24)	-			(9)	-	(12)	-	(12)	-		
%	0.41	-	0.38	-	*0.0805*	*Chi2*	0.42	-	0.31	-	0.46	-	*0.48*	*Chi2*
DLCO (mL/min/mmHg)	17.92	6.21	14.99	4.93	*0.0274*	*t-test*	17.92	6.21	14.91	4.82	15.11	5.18	*0.088*	*ANOVA*
DLCO (%)	78.3	24.35	63.9	18.96	*0.0053*	*t-test*	78.3	24.35	61.7	15.49	67.0	23.10	*0.0126*	*ANOVA*
**Significant reversibility = change in FEV1 of >200 mL & >12%*														

Table 113: Comparison of the results of lung physiology at Visit 3 according to PPTB status, only in subjects in CAO.

(n=86)	NPTB	sd	PPTB	sd	*p-value*	*test*	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
(n)	(22)		(64)				(22)		(38)		(26)			
Post BD FVC (L) -mean	2.81	0.957	3.08	1.104	*n/a*	*n/a*	2.81	0.957	3.15	1.075	2.97	1.158	*n/a*	*n/a*
Post BD FVC (L) -median	2.72	-	2.90	-	*0.4198*	*Wilcoxon*	2.72	-	3.09	-	2.76	-	*0.4935*	*Kwallis*
Post BD FVC (%) - mean	93.95	17.214	97.19	18.227	*0.4689*	*t-test*	93.95	17.214	97.03	19.253	97.42	16.985	*0.7676*	*ANOVA*
Post BD FVC (%) - median	96.00		97.00		*n/a*	*n/a*	96.00		97.00	-	97.50	-	*n/a*	*n/a*
Post BD FEV1 (L) -mean	1.63	0.637	1.63	0.746	*n/a*	*n/a*	1.63	0.637	1.64	0.793	1.62	0.687	*n/a*	*n/a*
Post BD FEV1 (L) - median	1.47	-	1.34	-	*0.6704*	*Wilcoxon*	1.47	-	1.36	-	1.32		*0.8704*	*Kwallis*
Post BD FEV1 (%) -mean	67.55	18.441	65.45	23.340	*n/a*	*n/a*	67.55	18.441	63.45	25.446	68.38	19.986	*n/a*	*n/a*
Post BD FEV1 (%) -median	68.50		65.00		*0.5861*	*Wilcoxon*	68.50		60.50		68.00		*0.4816*	*Kwallis*
Post BD FEV1:FVC - mean	57.72	11.273	53.36	12.870	*n/a*	*n/a*	57.72	11.273	51.30	12.679	56.38	12.792	*n/a*	*n/a*
Post BD FEV1:FVC - median	58.84	-	56.81	-	*0.2408*	*Wilcoxon*	58.84	-	53.32	-	61.71	-	*0.1338*	*Kwallis*
Significant reversibility = change in FEV1 of >200 mL & >12%														

Table 114: Comparison of the results of whole body plethysmography data at Visit 3 according to PPTB status, only in subjects with CAO.

(n=83)	NPTB	sd	PPTB	sd	*p-value*	*test*	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
(n)	(21)		(62)				(21)		(37)		(25)			
TLC (L)- mean*	5.64	1.31	5.93	1.53	*0.4426*	*t-test*	5.64	1.31	6.04	1.36	5.76	1.77	*n/a*	*n/a*
TLC (L)- median	5.75	-	5.89	-	*n/a*	*n/a*	5.75#	-	6.00#	-	4.90#	-	*0.4384*	*Kwallis*
TLC (%)- mean#	105.81	14.02	106.61	18.73	*n/a*	*n/a*	105.81	14.02	107.97	21.06	104.60	14.79	*n/a*	*n/a*
TLC (%)- median	103.00		103.00	-	*0.9916*	*Wilcoxon*	103.00		102.00	-	106.00	-	*0.9962*	*Kwallis*
VC (L)- mean#	2.77	0.76	2.77	0.91	*n/a*	*n/a*	2.77	0.76	2.78	0.89	2.75	0.95	*n/a*	*n/a*
VC (L)- median	2.60	-	2.68	-	*0.8463*	*Wilcoxon*	2.60	-	2.82	-	2.50	-	*0.9465*	*Kwallis*
VC (%)- mean*	89.00	12.07	83.97	14.15	*0.1469*	*t-test*	89.00	12.07	82.16	13.92	86.64	14.34	*0.1595*	*ANOVA*
VC (%)- median	91.00	-	85.00	-	*n/a*	*n/a*	91.00	-	84.00	-	88.00		*n/a*	*n/a*
IC (L)- mean*	2.42	0.60	2.07	0.56	*0.0172*	*t-test*	2.42	0.60	2.04	0.52	2.11	0.63	*0.0542*	*ANOVA*
IC (L)- median	2.36	-	2.08	-	*n/a*	*n/a*	2.36	-	2.08	-	2.04	-	*n/a*	*n/a*
IC (%)- mean#	116.95	21.04	96.42	26.59	*n/a*	*n/a*	116.95	21.04	94.00	28.86	100.00	22.91	*n/a*	*n/a*
IC (%)- median	119.00	-	93.00	-	*0.0002*	*Wilcoxon*	119.00	-	92.00	-	97.00	-	*0.0004*	*Kwallis*
FRC (L)- mean#	3.17	0.94	3.86	1.24	*n/a*	*n/a*	3.17	0.94	4.00	1.15	3.65	1.36	*n/a*	*n/a*
FRC (L)- median	2.80	-	3.56	-	*0.0206*	*Wilcoxon*	2.80	-	3.77	-	3.01	-	*0.0174*	*Kwallis*
FRC (%)- mean#	109.62	23.83	127.00	33.34	*n/a*	*n/a*	109.62	23.83	130.97	35.39	121.12	29.76	*n/a*	*n/a*
FRC (%)- median	105.00	-	120.50	-	*0.0260*	*Wilcoxon*	105.00	-	122.00	-	114.00	-	*0.0464*	*Kwallis*
ERV (L)- mean#	0.35	0.35	0.70	0.51	*n/a*	*n/a*	0.35	0.35	0.73	0.51	0.64	0.52	*n/a*	*n/a*

ERV (L)- median	0.21	-	0.59	-	*0.0023*	*Wilcoxon*	0.21	-	0.67		0.48	-	*0.0069*	*Kwallis*
(n=83)	**NPTB**	**sd**	**PPTB**	**sd**	***p-value***	***test***	**NPTB**	**sd**	**DPTB**	**sd**	**PrPTB**	**sd**	***p-value***	***test***
(n)	(21)		(62)				(21)		(37)		(25)			
ERV (%)- mean#	38.29	28.97	70.82	42.68	*n/a*	*n/a*	38.29	28.97	72.11	41.92	68.92	44.58	*n/a*	*n/a*
ERV (%)- median	26.00	-	66.50	-	*0.0012*	*Wilcoxon*	26.00	-	69.00		58.00	-	*0.0047*	*Kwallis*
RV (L)- mean#	2.86	0.81	3.16	1.01	*n/a*	*n/a*	2.86	0.81	3.27	1.00	3.01	1.01	*n/a*	*n/a*
RV (L)- median	2.60	-	2.94	-	*0.2184*	*Wilcoxon*	2.60	-	3.04	-	2.61	-	*0.2047*	*Kwallis*
RV (%)- mean#	141.57	34.26	152.25	50.02	*n/a*	*n/a*	141.57	34.26	157.89	55.98	143.88	39.22	*n/a*	*n/a*
RV (%)- median	135.00	-	137.00	-	*0.5715*	*Wilcoxon*	135.00	-	141.00	-	135.00	-	*0.6812*	*Kwallis*
RV:TLC – mean*	50.81	6.98	53.44	8.82	*0.2193*	*t-test*	50.81	6.98	54.14	10.14	52.40	6.45	*0.3446*	*ANOVA*
RV:TLC - median	52.00	-	54.00		*n/a*	*n/a*	52.00	-	56.00		52.00	-	*n/a*	*n/a*
	(n=20)		(n=62)				(n=20)		(n=37)		(n=25)			
TV – mean#	0.66	0.20	0.76	0.32	-	-	0.66	0.20	0.70	0.21	0.84	0.42	-	-
TV- median	0.65	-	0.70		-	-	0.65	-	0.69	-	0.79		-	-

** Parametric data*
 # Non-parametric data

Appendix 8 - Results of Lung Imaging, only for Subjects with Chronic Airflow Obstruction

Table 115: Bronchial wall area (Pi10) according to PPTB status, only subjects with CAO: All subjects, NPTB vs PPTB.

	All	sd	NPTB	sd	PPTB	sd	*p-value*	*test*
(n)	(85)		(21)		(64)			
Pi10								
Mean	2.50	0.580	2.51	0.606	2.50	0.576	*0.9756*	*Wilcoxon*
Median	2.49		2.49		2.49			

Table 116: Bronchial wall area (Pi10) according to PPTB status, only subjects with CAO: three-group analysis.

(n=85)	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
(n)	(21)		(38)		(26)			
Pi10								
Mean	2.51	0.606	2.46	0.642	2.56	0.470	*0.351*	*Kwallis*
Median	2.49		2.36		2.61			

Table 117: Lung and lobar density (average Hounsfield Units - HU) at total lung capacity, according to PPTB status, only subjects with CAO.

	All	sd	NPTB	sd	PPTB	sd	p-value (test)	NPTB	sd	DPTB	sd	PrPTB	sd	p-value (test)
(n)	(77)		(19)		(58)			(19)		(34)		(24)		
Total Lung#														
mean HU	-849.88	32.03	-844.14	31.94	-851.76	32.11	*0.3629*	-844.14	31.94	-853.66	31.75	-849.07	33.1	*0.4813*
median HU	-852.54		-852.41		-852.64		*Wilcoxon*	-852.41		-856.52		-848.76		*Kwallis*
Left Lung #														
mean HU	-849.88	35.16	-844.5	33.3	-851.64	35.85	*0.4183*	-844.5	33.3	-854.01	35.99	-848.28	36.14	*0.3908*
median HU	-859.52		-859.68		-856.89		*Wilcoxon*	-859.68		-861.8		-847.14		*Kwallis*
LUL#														
mean HU	-854.35	35.64	-849.83	33.42	-855.83	36.5	*0.4857*	-849.83	33.42	-856.58	38.76	-854.76	33.83	*0.6818*
median HU	-859.97		-850.12		-860.27		*Wilcoxon*	-850.12		-859.11		-860.5		*Kwallis*
LLL#														
mean HU	-842.69	37.78	-835.59	36.86	-845.02	38.11	*0.2718*	-835.59	36.86	-848.42	36.99	-840.2	39.93	*0.2298*
median HU	-849.66		-839.46		-850.04		*Wilcoxon*	-839.46		-853.11		-845.95		*Kwallis*
Right Lung*														
mean HU	-849.67	30.76	-843.68	31.02	-851.63	30.68	*0.3692*	-843.68#	31.02	-853.18#	30.75	-849.44#	31.12	*0.5733*
median HU	-854.27		-845.29		-854.43		*Wilcoxon*	-845.29		-854.94		-844.85		*Kwallis*
RUL*														
mean HU	-850.54	30.22	-850.9	34.02	-850.42	29.19	*0.952*	-850.9	34.02	-851.72	28.81	-848.57	30.25	*0.9262*
median HU	-853.56		-858.68		-853.29		*t-test*	-858.68		-850.33		-854.1		*ANOVA*
RML *														

	All	sd	NPTB	sd	PPTB	sd	p-value (test)	NPTB	sd	DPTB	sd	PrPTB	sd	p-value (test)
mean HU	-860.68	30.64	-852.84	28.4	-863.25	31.14	*0.2007*	-852.84	28.4	-865.7	31.4	-859.79	31.1	*0.3417*
median HU	-857.97		-850.08		-861.75		*t-test*	-850.08		-866.37		-857.65		*ANOVA*
RLL #														
mean HU	-841.44	41.26	-829.82	34.54	-845.24	42.82	*0.0527*	-829.82	34.54	-845.52	46.44	-844.85	38.07	*0.1318*
median HU	-843.11		-829.47		-850.44		*Wilcoxon*	-829.47		-852.94		-841.88		*Kwallis*
# - non-parametric variables **** -parametric variables***														

Table 118: Lung and lobar density (average Hounsfield Units - HU) at residual volume, according to PPTB status, only subjects with CAO.

	All	sd	NPTB	sd	PPTB	sd	p-value (test)	NPTB	sd	DPTB	sd	PrPTB	sd	p-value (test)
(n)	(77)		(19)		(58)			(19)		(34)		(24)		
Total Lung*														
mean HU	-747.4	68.53	-716.33	83.9	-757.58	60.1	*0.0217 t-test*	-716.33	83.9	-763.57	58.05	-749.11	63.15	*0.0526 ANOVA*
Left Lung *			(n=19)		(n=58)			(n=19)		(n=34)		(n=24)		
mean HU	-742.64	72.3	-713.69	82.54	-752.12	66.69	*0.0436 t-test*	-713.69	82.54	-757.8	66.28	-744.09	67.84	*0.1019 ANOVA*
LUL#			(n=19)		(n=58)			(n=19)		(n=34)		(n=24)		
mean HU	-759.13	72.79	-730.09	86.43	-768.72	65.8	*0.0763 Wilcoxon*	-730.09	86.43	-774.53	64.45	-760.5	68.19	*0.1676 Kwallis*
median HU	-773.91		-766.32		-781.84			-766.32		-787.07		-772.52		
LLL#			(n=18)		(n=58)			(n=18)		(n=34)		(n=24)		
mean HU	-723.33	71.8	-703.62	68.7	-729.44	72.22	*0.2172 WIlcoxon*	-703.62	68.7	-735.18	74.08	-721.32	70.24	*0.3206 ANOVA*
median HU	-712.67		-694.77		-713.02		*[0.1844] [t-test]*	-694.77		-727.97		-709.46		
Right Lung*	(n=75)		(n=18)		(n=57)			(n=18)		(=34)		(n=23)		
mean HU	-755.67	59.56	-729.04	68.5	-764.08	54.44	*0.0286 t-test*	-729.04	68.5	-768.26	54.16	-757.9	55.46	*0.0746 ANOVA*
RUL*			(n=18)		(n=57)			(n=18)		(=34)		(n=23)		
mean HU	-762.8	61.28	-746.19	70.96	-768.04	57.59	*0.1892 t-test*	-746.19	70.96	-775.34	56.66	-757.26	58.51	*0.2332 ANOVA*
RML *			(n=18)		(n=57)			(n=18)		(=34)		(n=23)		
mean HU	-791.17	55.96	-766.35	68.91	-799.01	49.35	*0.0299 t-test*	-766.35	68.91	-800.83	52.1	-796.32	45.99	*0.0918 ANOVA*
RLL *			(n=18)		(n=57)			(n=18)		(=34)		(n=23)		
mean HU	-725.46	77.02	-685.49	76.35	-738.09	73.44	*0.0106 t-test*	-685.49	76.35	-740.03	76.61	-735.22	70.09	*0.0379 ANOVA*

 # - non-parametric variables
**** -parametric variables***

Table 119: Comparison of emphysema scores (using -950HU cut-point) according to PPTB status, only subjects with CAO

	All	sd	NPTB	sd	PPTB	sd	*p-value*	*test*	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
(n)	(77)		(19)		(58)				(19)		(34)		(24)			
Total*																
mean	27.09	8.68	25.72	6.6	27.54	9.26	*0.4308*	*t-test*	25.72	6.6	28.91	7.95	25.6	10.74	*0.2652*	*ANOVA*
Left Lung*																
mean	27.06	9.01	25.98	6.83	27.41	9.64	*0.5532*	*t-test*	25.98	6.83	28.76	8.18	25.5	11.3	*0.3374*	*ANOVA*
LUL*																
mean	28.66	9.44	27.14	7.14	29.16	10.08	*0.4232*	*t-test*	27.14#	7.14	30.78#	9.03	26.85#	11.19	*0.1356*	*Kwallis*
median	28.82		26.52		29.45				26.52		30.11		24.77			
LLL#																
mean	24.78	9.81	23.7	8.61	25.13	10.22	*0.5468*	*WilcoxonRS*	23.7	8.61	26.19	8.81	23.64	11.99	*0.2326*	*Kwallis*
median	22.95		22.44		23.27				22.44		26.02		20.31			
Right Lung*																
mean	27.15	8.85	25.45	6.53	27.71	9.47	*0.3384*	*t-test*	25.45	6.53	29.17	8.64	25.63	10.35	*0.1334*	*Kwallis*
	26.35		26.35		26.37				26.35		29.87		22.83			
RUL*																
mean	28.36	9.16	27.33	7.53	28.7	9.66	*0.5768*	*t-test*	27.33	7.53	30.41	9.48	26.27	9.59	*0.2049*	*ANOVA*
RML*																
mean	28.26	9.72	26.11	7.55	28.97	10.3	*0.2679*	*t-test*	26.11	7.55	30.38	10.24	26.97	10.26	*0.229*	*ANOVA*
RLL#																
mean	25.35	10.55	22.3	7.4	26.35	11.27	*0.1161*	*Wilcoxon*	22.3	7.4	27.66	10.35	24.51	12.45	*0.064*	*Kwallis*
median	24.14		22.26		25.5				22.26		27.29		21.21			

(values indicate the % of lung parenychyma below -950HU)

 # - non-parametric variables ** -parametric variables*

Table 120: Comparison of gas trapping scores (using -860HU cut-point) according to PPTB status, only subjects with CAO.

	All	sd	NPTB	sd	PPTB	sd	*p-value*	*test*	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
(n)	**(77)**		**(19)**		**(58)**				**(28)**		**(35)**		**(31)**			
Total*									(n=19)		(n=34)		(n=24)			
mean	35.55	15.27	30.07	13.43	37.35	15.51	*0.0709*	*t-test*	30.07	13.43	39.33	15.01	34.55	16.08	*0.0974*	*ANOVA*
Left Lung#	(n=77)		(n=19)		(n=58)				(n=19)		(n=34)		(n=24)			
mean	34.21	16.3	29	13.57	35.92	16.85	*0.1188*	*Wilcoxon*	29	13.57	37.82	16.87	33.23	16.82	*0.1911*	*Kwallis*
median	30.67		25		32.57				25		36.52		30.69			
LUL*	(n=77)		(n=19)		(n=58)				(n=19)		(n=34)		(n=24)			
mean	37.77	16.76	31.59	13.5	39.79	17.32	*0.0636*	*t-test*	31.59	13.5	42.07	17.53	36.57	16.85	*0.0827*	*ANOVA*
LLL#	(n=76)		(n=18)		(n=58)				(n=18)		(n=34)		(n=24)			
mean	29.18	17.56	25.4	15.36	30.35	18.15	*0.3992*	*Wilcoxon*	25.4	15.36	31.89	18.58	28.18	17.68	*0.5598*	*Kwallis*
median	22.5		22.64		22.5				22.64		25.84		22.01			
Right Lung*	(n=75)		(n=18)		(n=57)				(n=18)		(n=34)		(n=23)			
mean	37.11	14.94	30.76	13.91	39.12	14.8	*0.0377*	*t-test*	30.76	13.91	40.74	14.76	36.72	14.81	*0.0697*	*ANOVA*
RUL#	(n=75)		(n=18)		(n=57)				(n=18)		(n=34)		(n=23)			
mean	39.16	15.8	33.82	14.65	40.85	15.89	*0.1041*	*Wilcoxon*	33.82*	14.65	43.23*	16.76	37.34*	14.15	*0.0984*	*ANOVA*
	38.25		30.75		39.44				30.75		44.37		38.25			
RML*	(n=75)		(n=18)		(n=57)				(n=18)		(n=34)		(n=23)			
mean	44.34	16.22	37.77	16.84	46.42	15.6	*0.0478*	*t-test*	37.77	16.84	47.21	16.46	45.25	14.51	*0.129*	*ANOVA*

	All	sd	NPTB	sd	PPTB	sd	*p-value* *test*	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value* *test*
	41.72		34.41		46.5			34.41		49.05		43.53		
RLL#	(n=75)		(n=18)		(n=57)			(n=18)		(n=34)		(n=23)		
mean	30.95	17.57	22.62	14.48	33.59	17.75	*0.0079* *Wilcoxon*	22.62	14.48	34.8	17.81	31.78	17.91	*0.0212* *Kwallis*
median	25.74		19.67		28.39			19.67		29.89		28.25		

(values indicate the % of lung parenychyma below 860HU)
 # - non-parametric variables
** -parametric variables*

Table 121: Comparison of corrected gas trapping scores[§] according to PPTB status, only subjects with CAO.

	All	sd	NPTB	sd	PPTB	sd	*p-value*	*test*	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
(n)	(77)		(19)		(58)				(19)		(34)		(24)			
Total*																
mean	8.46	10.93	4.35	9.14	9.81	11.21	0.0583	t-test	4.35	9.14	10.42	11.85	8.95	10.4	0.1479	ANOVA
median	6.14		4.08		8.52				4.08		10.19		6.51		(0.1197	Kwallis)
Left Lung*	(n=77)		(n=19)		(n=58)				(n=19)		(n=34)		(n=24)			
mean	7.16	11.67	3.01	9.87	8.51	11.97	0.0746	t-test	3.01	9.87	9.06	13.23	7.73	10.15	0.188	ANOVA
	3.9		2.36		7				2.36		9.2		4.33		(0.1672	Kwallis)
LUL*	(n=77)		(n=19)		(n=58)				(n=19)		(n=34)		(n=24)			
mean	9.11	12.34	4.45	10.18	10.64	12.67	0.0572	t-test	4.45	10.18	11.29	13.86	9.71	11	0.1475	ANOVA
median	7.87		1.45		9.16				1.45		10.17		7.5		(0.1216	Kwallis)
LLL*	(n=76)		(n=18)		(n=58)				(n=18)		(n=34)		(n=24)			
mean	4.29	12.3	1.3	9.73	5.22	12.92	0.2399	t-test	1.3	9.73	5.7	14.56	4.54	10.42	0.4733	ANOVA
median	2.62		-0.13		3.55				-0.13		6.25		3.21		(0.5387	Kwallis)
Right Lung*	(n=75)		(n=18)		(n=57)				(n=18)		(n=34)		(n=23)			
Mean	9.65	10.8	4.97	9.5	11.12	10.84	0.0343	t-test	4.97	9.5	11.57	11.08	10.46	10.68	0.1002	ANOVA
	8.9		3.85		10.23				3.85		11.91		9.83		(0.0755	Kwallis)
RUL*	(n=75)		(n=18)		(n=57)				(n=18)		(n=34)		(n=23)			
Mean	10.52	11.47	6.15	10.02	11.9	11.64	0.0633	t-test	6.15	10.02	12.82	12	10.54	11.19	0.1367	ANOVA
	9.74		6.03		12.98				6.03		15.25		11.14		(0.1156	Kwallis)
RML*	(n=75)		(n=18)		(n=57)				(n=18)		(n=34)		(n=23)			
mean	15.67	12.1	11.26	11.99	17.06	11.9	0.0759	t-test	11.26	11.99	16.83	12.66	17.41	10.94	0.2058	ANOVA
	16.26		11.26		17.1				11.26		17.39		17.1		(0.1651	Kwallis)
RLL#	(n=75)		(n=18)		(n=57)				(n=18)		(n=34)		(n=23)			
mean	5.27	11.94	0.03	9.69	6.93	12.17	0.0317	t-test	0.03	9.69	7.14	12.86	6.61	11.36	0.0552	Kwallis
median	2.41		-1.54		3.94				-1.54		5.33		3.94			

(values indicate the adjusted % of lung parenchyma below threshold)
§- Corrected Gas Trapping score = (860 HU score at RV – 950HU score at TLC)
 # - non-parametric variables
** -parametric variables*

Table 122: Comparison of fibrosis scores (using -200HU cut-point) according to PPTB status, only subjects with CAO.

	All	sd	NPTB	sd	PPTB	sd	*p-value*	*test*	NPTB	sd	DPTB	sd	PrPTB	sd	*p-value*	*test*
(n)	(77)		(19)		(58)				(19)		(34)		(24)			
Total#																
mean	2.23	0.57	2.03	0.41	2.29	0.61	*0.1107*	*Wilcoxon*	2.03	0.41	2.43	0.64	2.1	0.502	*0.0312*	*Kwallis*
median	2.15		2		2.18				2		2.28		2.13			
Left Lung#																
mean	2.16	0.62	2	0.45	2.21	0.67	*0.277*	*Wilcoxon*	2	0.45	2.31	0.68	2.07	0.63	*0.1697*	*Kwallis*
median	2.06		1.91		2.11				1.91		2.14		2.11			
LUL#																
mean	2.1	0.76	1.86	0.38	2.18	0.84	*0.1978*	*Wilcoxon*	1.86	0.38	2.41	1	1.85	0.375	*0.0393*	*Kwallis*
median	1.9		1.84		1.99				1.84		2.21		1.88			
LLL#																
mean	2.27	0.76	2.2	0.6	2.3	0.81	*0.9717*	*Wilcoxon*	2.2	0.6	2.3	0.73	2.29	0.93	*0.9195*	*Kwallis*
median	2.16		2.16		2.16				2.16		2.16		2.15			
Right Lung#																
mean	2.3	0.65	2.06	0.39	2.38	0.70	*0.1161*	*Wilcoxon*	2.06	0.39	2.56	0.7	2.13	0.625	*0.0066*	*Kwallis*
median	2.17		2.02		2.18				2.02		2.34		2.03			
RUL#																
mean	2.47	1.26	1.85	0.41	2.67	1.38	*0.0033*	*Wilcoxon*	1.85	0.41	2.89	1.2	2.36	1.574	*0.0002*	*Kwallis*
median	2.1		1.8		2.2				1.8		2.45		1.93			
RML#																
mean	1.87	0.74	1.8	0.54	1.89	0.79	*0.9623*	*Wilcoxon*	1.8	0.54	1.98	0.94	1.77	0.517	*0.6817*	*Kwallis*
median	1.85		1.87		1.83				1.87		1.87		1.65			
RLL#																
mean	2.46	0.87	2.4	0.53	2.48	0.96	*0.8408*	*Wilcoxon*	2.4	0.53	2.69	1.14	2.18	0.536	*0.0819*	*Kwallis*
median	2.29		2.32		2.28				2.32		2.31		2.03			

values indicate the % of lung parenychyma above -200HU
 # - non-parametric variables

Table 123: Comparison of average HU at RV between NPTB and DPTB groups*, only in subject with CAO.

(n=53)	***p-value***	***test***
Total Mean HU	*0.0194*	*t-test*
Left Lung Mean HU	*0.0384*	*t-test*
LUL Mean HU	*0.0585*	*Wilcoxon*
LLL Mean HU	*0.1405*	*t-test*
Right Lung Mean HU	*0.0279*	*t-test*
RUL Mean HU	*0.11255*	*t-test*
RML Mean HU)	*0.048*	*t-test*
RLL Mean HU	*0.018*	*t-test*
**(i.e. PrPTB group excluded)* *See above tables for values*		

Table 124: Comparison of emphysema score between NPTB and DPTB*, only in subjects with CAO.

(n=53)	***p-value***	***test***
Total	*0.1436*	*t-test*
Left Lung	*0.2163*	*t-test*
LUL	*0.0915*	*Wilcoxon*
LLL	*0.214*	*Wilcoxon*
Right Lung	*0.1091*	*t-test*
RUL	*0.2305*	*t-test*
RML	*0.1178*	*t-test*
RLL	*0.0215*	*Wilcoxon*
**(i.e. PrPTB group excluded)* *See above tables for values*		

Table 125: Comparison of gas trapping scores (at -860HU cut-point) between NPTB and DPTB groups, only in subjects with CAO.

(n=53)	***p-value***	***test***
Total	*0.0299*	*t-test*
Left Lung	*0.072*	*WilcoxonRS*
LUL	*0.0284*	*t-test*
LLL	*0.308*	*WilcoxonRS*
Right Lung	*0.02211*	*t-test*
RUL	*0.0501*	*t-test*
RML	*0.0564*	*t-test*
RLL	*0.0071*	*WilcoxonRS*
**(i.e. PrPTB group excluded)* *See above tables for values*		

Table 126: Comparison of corrected gas trapping scores between NPTB and DPTB groups, only in subjects with CAO.

(n=53)	***p-value***	***test***
Total	*0.059*	*t-test*
Left Lung	*0.0883*	*t-test*
LUL	*0.0653*	*t-test*
LLL	*0.2555*	*t-test*
Right Lung	*0.0371*	*t-test*
RUL	*0.0495*	*t-test*
RML	*0.1308*	*t-test*
RLL	*0.0452*	*t-test*
**(i.e. PrPTB group excluded)* *See above tables for values*		

Appendix 9: Abstracts presented at conferences

The following four abstracts were presented in the form of posters. Abstracts 1 and 2 were presented at the American Thoracic Society Conference May 2014 (San Diego); while abstracts 3 and 4 were presented at the European Respiratory Society Conference September 2014 (Munich).

1. Abstract 1

Assessment of previous tuberculosis status in adults using questionnaires, chest X-rays and CT scans

Brian Allwood[1], Jonathan Goldin[2], Qonita Said-Hartley[1], Richard van Zyl-Smit[1], Greg Calligaro[1], Aliasgar Esmail[1], Nulda Beyers[3], Eric D Bateman[1].

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Introduction:

Determining with certainty whether an individual has previously had pulmonary TB (PPTB) is important for clinicians and in research. A record of bacteriologically-confirmed PTB is often not available and PPTB status is based on the patient history and/or chest X-ray. We compared history, chest X-rays and CT scans to develop a method to establish with greatest confidence the absence of PPTB.

Subjects and Methods:

The study population comprised adults aged 40yrs and older diagnosed with obstructive lung disease in a large community-based prevalence survey in Cape Town, South Africa, performed using the BOLD (Burden of Obstructive Lung Disease) methodology. PPTB status was assessed with two administered questionnaires, standard chest X-rays and high resolution CT scans of the chest reported by experienced readers.

Results:

One hundred and four subjects completed the assessments. Agreement between the two questionnaires was excellent (kappa value 0.96), an episode of PPTB being reported in 41 of 107 (38.3%) of subjects using the BOLD questionnaire, and in 39 of 104 (36.4%) with the PTbQ (Previous TB Questionnaire). Chest X-ray reports identified evidence of PPTB in 45 of 104 of subjects (43.3%) and between-reader agreement was good (Kappa value 0.73). There was moderate concordance between findings of questionnaires and chest X-rays (80.8%; kappa value 0.60). Changes compatible with PPTB were identified on chest CT scans in 68.3% of subjects (71 of 104) and between-reader agreement was moderate (Kappa value 0.43).

Using the combination of PTbQ and CT scan assessment as a composite definition, questionnaires alone had a sensitivity of 53.4% for PPTB and a 32.7% false negative rate. Expert chest X-ray read alone had a sensitivity of 57.5% and a specificity of 90.3% for PPTB.

Interpretation:

Both clinical history and chest X-ray markedly underestimate the prevalence of PPTB in patients with COPD. The combination of a structured questionnaire and a CT scan is more reliable for situations in which PPTB needs to be ruled out with relatively greater confidence.

2. Abstract 2

Mechanism of Airflow Obstruction in Tuberculosis-associated Obstructive Pulmonary Disease (TOPD)

Brian Allwood[1], Rencia Gillespie[1], Maya Galperin –Aizenberg[2], Mary Bateman[1], Helena Olckers[1], Luis Taborda-Barata[3], Greg Calligaro[1], Qonita Said-Hartley[1], Richard van Zyl-Smit[1], Christopher B Cooper[4], Eva van Rikxoort[5], Jonathan Goldin[4], Nulda Beyers[6], Eric D Bateman[1]

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INTRODUCTION

Epidemiological studies in populations with a high burden of pulmonary tuberculosis (PTB) suggest an association between PTB and the development of chronic airflow obstruction (AFO). The mechanisms responsible for AFO likely include airway narrowing (from bronchiolitis, bronchiectasis or persistent low-grade inflammation associated with healed PTB) and reduced lung elastic recoil from coexistent emphysema. These possibilities give rise to different opinions on whether Tuberculosis-associated Obstructive Pulmonary Disease (TOPD) should be viewed as a separate phenotype within the broad definition of Chronic Obstructive Pulmonary Disease (COPD). We performed dynamic quantitative CT lung imaging and measured lung physiology in patients with healed PTB and AFO to examine relationships between structural abnormalities and physiological function.

METHODS

The study population comprised subjects with chronic AFO identified during a population-based COPD prevalence survey performed in two low-middle-income suburbs of Cape Town, South Africa in 2005 using Burden Obstructive Lung Disease (BOLD) methodology. Beginning 2010, attempts were made to trace all subjects and invite them to participate in this follow-up study. Detailed questionnaires, lung physiology (including spirometry, plethysmography and CO diffusion capacity) as well as standardized low-dose quantitative chest CT scans were performed to assess bronchial anatomy and the presence of emphysema (HU<-950), gas trapping (HU<-860) and fibrosis (HU>-200).

RESULTS One hundred and seven of 196 eligible subjects (54.6%) diagnosed with AFO in the 2006 survey were enrolled. Lung physiology was assessed in 103 and CT scans suitable for quantitative analysis in 94 subjects. AFO (defined as FEV_1/FVC <0.70) was confirmed in only 86 subjects (83.5%) Based on history and CT scans, subjects were categorized as “No previous TB ” (NPTB; n=31, 30.1%), “Probable previous TB” (PPTB; n=33, 32.0%) or “Definite Previous TB” (DPTB; n=39, 37.8%). Subjects with DPTB had 16.3% lower DLCO (95 CI: -26.3 to -6.3%; P=0.002) and 22.2% lower IC (95% CI: -33.9 to -10.5; P<0.001) than NPTB subjects. Multivariate analysis confirmed that DPTB subjects had 6.5% higher gas-trapping score (95% CI: 1.34 to

11.60; P=0.014), and 0.33% higher fibrosis score (95% CI: 0.09 to 0.57; P=0.007), and 3.5% higher emphysema scores (95% CI: 0.21 – 6.82; P=0.038) than subjects with NPTB.

CONCLUSION

This structure-function evaluation of persons with TOPD, ie: chronic AFO and evidence of previous (healed) PTB confirms that patients with the latter risk factor should be considered a distinct clinical phenotype of COPD, characterized by lower DLCO, but more gas trapping confirmed by both lung physiology and CT scans.

3. Abstract 3

Five-year lung function follow-up of subjects diagnosed with COPD in the South African Burden of Obstructive Lung Disease (BOLD) Survey

Brian Allwood[1] Rencia Gillespie[1], Mary Bateman[1] Helena Olckers[1], Luis Taborda-Barata[2], Greg Calligaro[1], Richard van Zyl-Smit[1], Nulda Beyers[3], Eric D Bateman[1]

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BACKGROUND:

A community-based prevalence survey performed in Cape Town in 2005, using the Burden of Obstructive Lung Disease (BOLD) methodology estimated the prevalence of COPD to be 24% among adults aged 40 years and older**.** There is limited data on the natural history and progression of COPD in an African cohort.

AIMS:

To perform five-year follow-up of all subjects identified as having COPD in the previous BOLD study.

METHODS:

We traced all subjects previously identified COPD. Participants were invited to participate, and spirometry was performed using the same handheld spirometers in the BOLD study

RESULTS:

Of the 196 eligible subjects, 45 (23%) had died, 11 (6%) had moved away, 33 (17%) declined participation or had medical exclusions factors (e.g. dementia) and 1 was unable to perform spirometry. Of the 106 (54%) subjects included, the median age was 63y and 46% were men (49 subjects).

The cause of death was unknown in 21 subjects (47%), due to respiratory disease in 8 (18%), cardiovascular disease in 10 (22%), and miscellaneous causes in 6 (13%). On multivariate analysis, only age and GOLD stage 4 COPD were significantly associated with death.

Post-bronchodilator spirometry showed 16 of 106 (15%) had no airflow obstruction (FEV1:FVC ratio ≥ 0.7). The remaining 90 subjects (85%) had a median decline in FEV1 of 28.9ml per year (SD 59.7ml/yr), with no difference in decline between GOLD stages. The median decline in FVC was -75ml, and was significantly greater in GOLD stage 1 (-350ml) compared with GOLD stages 2 or 3 (-80ml & +140ml respectively; $p<0.01$).

Of the subjects with current obstruction, 58 (64%) remained in the same GOLD stage, while 21 (23%) had deteriorated and 11 (12%) improved a GOLD stage.

CONCLUSIONS:

Interval follow-up of the BOLD COPD cohort revealed high mortality and variable disease progression, but also potential diagnostic inaccuracy of BOLD spirometry in a community survey.

4. Abstract 4

Assessment of the accuracy of Burden of Obstructive Lung Disease (BOLD) methodology in estimating prevalence of COPD

Brian Allwood[1] Rencia Gillespie[1], Mary Bateman[1] Helena Olckers[1], Luis Taborda-Barata[2], Greg Calligaro[1], Richard van Zyl-Smit[1], Nulda Beyers[3], Eric D Bateman[1]

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BACKGROUND:

The Burden of Obstructive Lung Disease (BOLD) methodology is used widely to estimate the prevalence of COPD in different communities. The accuracy of these estimates remains uncertain but is important for policy and planning

AIMS:

To assess the BOLD methodology for accuracy of both diagnosis and spirometry, in a local cohort.

METHODS:

We performed a detailed five-year follow-up of all subjects labeled COPD in the Cape Town BOLD study (2005), assessing for possibility of asthma and performance of the EasyOne ndd™ handheld spirometer.

RESULTS:

Of the 196 eligible subjects, 45 (23%) had died, and 45 had either moved, declined or were medically excluded (e.g. dementia), 106 (54%) were included. Sixteen subjects (15%) had FEV1:FVC ratio ≥ 0.7 (i.e. non-obstructed) after bronchodilator. Using the lower limit of normal definition, a further 11 subjects (10%) were non-obstructed, 7 of whom were >70years old.

Using both conservative and liberal definitions, the estimated overall prevalence of asthma ranged between 10–18%; being 6–13% for subjects without current obstruction (n=16); 11–19% for those with current obstruction (n=90); and 10–26% for those with both obstruction and bronchodilator reversibility (n=31).

When performed concurrently with handheld spirometry, office spirometry FEV1 differed by more than 150ml in 22% of subjects, and resulted in misclassification of COPD status in 17%. [Bland-Altman: mean diff=41ml; sd 146ml; 95%CI: -250ml: +333ml]

Between visit variability (<1 month apart) using handheld spirometry showed a change in COPD classification in 11 subjects (20%), with 29% having FEV1 values differing by >150ml. [Bland-Altman: mean diff = 18ml; sd 220ml; 95%CI: -0.422ml : +0.458ml]

CONCLUSIONS:

The BOLD methodology likely overestimates the burden of COPD due to use of the fixed-ratio definition of COPD; inclusion of asthmatics and variability of prescribed handheld spirometers.